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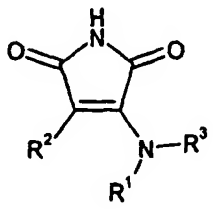
(54) Title: PYRROLE-2,5-DIONE DERIVATIVES FOR THE TREATMENT OF DIABETES



(I)

(57) Abstract: A method for the treatment of conditions associated with a need for inhibition of GSK-3, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, wherein R^1 is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic or non-aromatic ring; R^2 is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, with the proviso that R^2 is not 3-indolyl or a fused-ring derivative of 3-indolyl; R^3 is hydrogen, or R^1 and R^3 together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocyclic ring; to a human or non-human mammal in need thereof.

PYRROLE-2,5-DIONE DERIVATIVES FOR THE TREATMENT OF DIABETES

This invention relates to a novel method for the treatment and/or prophylaxis of conditions associated with a need for inhibition of glycogen synthase kinase-3 (GSK-3), especially diabetes, and chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, manic depression, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, and immunodeficiency; and to certain novel inhibitors of GSK-3 for use in such a method.

GSK-3 is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al* Eur. J. Biochem. **(107)** 519-527 (1980)). The α and β isoforms have a monomeric structure and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al* Biochemical Journal **(303)** 21-26 (1994)) and these two isoforms show good homology between species (e.g. human and rabbit GSK-3α are 96% identical).

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage.

The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J. Biochim. Biophys. Acta **(39)** 171-173 (1960), Parker P J *et al.*, Eur. J. Biochem. **(130)** 227-234 (1983), and Cohen P. Biochem. Soc. Trans. **(21)** 555-567 (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A K and Pandey S K Mol. and Cellular Biochem. **(182)** 135-141 (1998)).

Chen *et al* Diabetes **(43)** 1234-1241 (1994) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type II diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3α activity and insulin action (Nikoulina *et al* Diabetes 2000, 49 263-271). Overexpression of GSK-3β and constitutively active GSK-3β (S9A, S9E) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman *et al.*, PNAS **(93)** 10228-10233 (1996)) and overexpression of GSK-3β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), resulted in an impairment of insulin action (Eldar-Finkelman and Krebs PNAS **(94)** 9660-9664 (1997)). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin

resistance and type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman *et al.*, Diabetes **(48)** 1662-1666 (1999)).

GSK-3 has been shown to phosphorylate other proteins *in vitro* including the eukaryotic initiation factor eIF-2B at Serine^{540} (Welsh *et al.*, FEBS Letts **(421)** 125-130 (1998)). This phosphorylation results in an inhibition of eIF-2B activity and leads to a reduction in this key regulatory step of translation. In disease states, such as diabetes, where there is elevated GSK-3 activity this could result in a reduction of translation and potentially contribute to the pathology of the disease.

Several aspects of GSK-3 functions and regulation in addition to modulation of glycogen synthase activity indicate that inhibitors of this enzyme may be effective in treatment of disorders of the central nervous system. GSK-3 activity is subject to inhibitory phosphorylation by PI 3 kinase-mediated or Wnt-1 class-mediated signals that can be mimicked by treatment with lithium, a low mM inhibitor of GSK-3 (Stambolic V., Ruel L. and Woodgett J.R. Curr. Biol. 1996 6(12): 1664-8).

GSK-3 inhibitors may be of value as neuroprotectants in treatment of acute stroke and other neurotraumatic injuries. Roles for PI 3-kinase signalling through PKB/akt to promote neuronal cell survival are well established, and GSK-3 is one of a number of PKB/akt substrates to be identified that can contribute to the inhibition of apoptosis via this pathway (Pap & Cooper, (1998) J. Biol. Chem. **273:** 19929-19932). Evidence suggests that astrocytic glycogen can provide an alternative energy source to facilitate neuronal survival under conditions of glucose deprivation (for example see Ransom, B.R. and Fern, R. (1997) Glia **21:** 134-141 and references therein). Lithium is known to protect cerebellar granule neurons from death (D'Mello *et al.*, (1994) Exp. Cell Res. **211:** 332-338 and Volonte *et al* (1994) Neurosci. Letts. **172:** 6-10) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, (1998) Neuroreport 9(9): 2081-2084). Wnt-induced axonal spreading and branching in neuronal culture models has been shown to correlate with GSK-3 inhibition (Lucas & Salinas, (1997) Dev. Biol. **192:** 31-44) suggesting additional value of GSK-3 inhibitors in promoting neuronal regeneration following neurotraumatic insult.

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early event in neurodegenerative conditions such as Alzheimer's disease (AD), and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules, and promote microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M. J.Biol. Chem. 1997 272(40) 25326-32). β-catenin is phosphorylated by GSK-3 as part of a tripartite complex with axin, resulting in β-catenin being targetted for degradation (Ikeda *et al.*, (1998) EMBO J. **17:** 1371-1384). Inhibition of GSK-3 activity is a key mechanism by which cytosolic levels of catenin are stabilised and hence promote β–catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl (1999) Curr. Opin. Cell Biol. **11:** 233). Rapid onset AD mutations in presenilin-1 (PS-1) have been shown to decrease the cytosolic β-catenin

pool in transgenic mice. Further evidence suggests that such a reduction in available β-catenin may increase neuronal sensitivity to amyloid mediated death through inhibition of β-catenin-LEF-1/TCF transcriptional regulation of neuroprotective genes (Zhang *et al.*, (1998) Nature **395:** 698-702). A likely mechanism is suggested by the finding that mutant PS-1 protein confers decreased inactivation of GSK-3 compared with normal PS-1 (Weihl, C.C., Ghadge, G.D., Kennedy, S.G., Hay, N., Miller, R.J. and Roos, R.P.(1999) J. Neurosci. **19:** 5360-5369).

International Patent Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is lithium, but that there are serious drawbacks associated with this treatment. Whilst the precise mechanism of action of this drug for treatment of manic depression remains to be fully defined, current models suggest that inhibition of GSK-3 is a relevant target that contributes to the modulation of AP-1 DNA binding activity observed with this compound (see Manji *et al.*, (1999) J. Clin. Psychiatry **60** (suppl 2): 27-39 for review).

GSK-3 inhibitors may also be of value in treatment of schizophrenia. Reduced levels of β-catenin have been reported in schizophrenic patients (Cotter D, Kerwin R, al-Sarraji S, Brion JP, Chadwich A, Lovestone S, Anderton B, and Everall I. 1998 Neuroreport **9:**1379-1383) and defects in pre-pulse inhibition to startle response have been observed in schizophrenic patients (Swerdlow *et al* (1994) Arch. Gen. Psychiat. **51:** 139-154). Mice lacking the adaptor protein dishevelled-1, an essential mediator of Wnt-induced inhibition of GSK-3, exhibit both a behavioural disorder and defects in pre-pulse inhibition to startle response (Lijam N, Paylor R, McDonald MP, Crawley JN, Deng CX, Herrup K, Stevens KE, Maccaferri G, McBain CJ, Sussman DJ, and Wynshaw-Boris A. (1997) Cell **90:** 895-905). Together, these findings implicate deregulation of GSK-3 activity as contributing to schizophrenia. Hence, small molecule inhibitors of GSK-3 catalytic activity may be effective in treatment of this mood disorder.

The finding that transient β-catenin stabilisation may play a role in hair development (Gat *et al* Cell **(95)** 605-614(1998)) suggests that GSK-3 inhibitors could be used in the treatment of baldness.

Studies on fibroblasts from the GSK-3β knockout mouse (Hoeflich KP *et al.*, Nature 2000, **406**, 86-90) support a role for this kinase in positively regulating the activity of NFkB. This transcription factor mediates cellular responses to a number of inflammatory stimuli. Therefore, pharmacologic inhibition of GSK-3 may be of use in treating inflammatory disorders through the negative regulation of NFkB activity.

International Patent Application Number WO 98/16528 (Chiron Corporation) discloses certain purine derivatives as GSK-3 inhibitors. WO 99/47522 (University of British Colombia) discloses certain granulatimide derivatives as GSK-3β inhibitors. WO 99/65897 (Chiron Corporation) discloses certain pyrimidine and pyridine derivatives as GSK-3 inhibitors. WO 00/17184 (Mitsubishi Chemical Corporation) discloses certain hydroflavone derivatives as Tau protein kinase-1 (TPK-1) inhibitors, where Tau protein kinase is a synonym for GSK-3β. Co-pending International Patent Application No. WO 00/18758 Mitsubishi Chemical Corporation) discloses certain pyrimidone derivatives as TPK-1 inhibitors. Co-pending International Patent Applications Nos. WO 00/21927 and WO 00/38675 disclose certain pyrrole-2,5-dione derivatives as GSK-3 inhibitors. Co-

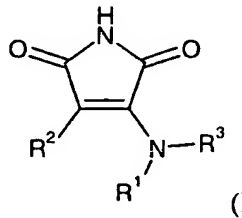
pending International Patent Application No. WO 01/09106 (SmithKline Beecham Plc) discloses certain 1,2,4-triazole derivatives as GSK-3 inhibitors.

Certain substitued 3-amino-4-arylmaleimides are disclosed in *J Amer Chem Soc* 1958, 80, 1385 which compounds have no disclosed pharmaceutical utility.

WO 00/06564 (Japan Tobacco Inc.) discloses certain 3-amino-4-(3-indolyl) maleimide derivatives as PKC-beta inhibitors.

We have now discovered that a series of 3-amino-4-arylmaleimides are particularly potent and selective inhibitors of GSK-3. These compounds are indicated to be useful for the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

Accordingly, in a first aspect, the present invention provides a method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof,
wherein;

R^1 is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic or non-aromatic ring;

R^2 is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, with the proviso that R^2 is not 3-indolyl or a fused-ring derivative of 3-indolyl;

R^3 is hydrogen, or,

R^1 and R^3 together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocylic ring;

to a human or non-human mammal in need thereof.

When R^1 is a substituted or unsubstituted carbocyclic aromatic ring, examples include phenyl.

When R^1 is a substituted or unsubstituted heterocyclic aromatic ring, examples include pyridinyl.

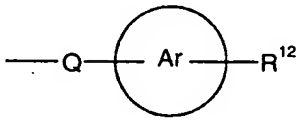
When R^1 is a substituted or unsubstituted carbocyclic aromatic ring which ring is fused to a substituted or unsubstituted carbocyclic non-aromatic ring, examples include indanyl.

When R^1 is a substituted or unsubstituted carbocyclic aromatic ring which ring is fused to a substituted or unsubstituted heterocyclic aromatic or non-aromatic ring, examples include benzothiazolyl, benzoxazolyl, indolinyl, quinolinyl, indolyl, benzothiazolinonyl, benzimidazolyl, benzimidazolinonyl, benzothiophenyl, benzofuranyl, indolinonyl, benzoxazinonyl, and benzoxazolinonyl.

When R^2 is a substituted or unsubstituted carbocyclic aromatic ring, examples include phenyl.

When R^1 and R^3 together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocylic ring, examples include indolinyl and tetrahydroquinolinyl.

When R^1 is a substituted carbocyclic aromatic ring or a substituted heterocyclic aromatic ring, suitable substituents include up to five groups independently selected from the list consisting of hydroxy, C_{1-6}alkoxy, di-(C_{1-6}alkyl)amino, cyano, substituted or unsubstituted C_{1-6}alkyl, carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkylaminocarbonyl, halo, carboxyC_{1-6}alkyloxy, C_{1-6}alkylamino, morpholinyl, hydroxyC_{1-6}alkylaminocarbonyl, (di-C_{1-6}alkylamino)carbonyl, C_{1-6}alkoxyC_{1-6}alkylaminosulphonyl, C_{1-6}alkylaminosulphonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonylamino, (perfluoroC_{1-6}alkyl)carbonylamino, C_{1-6}alkylthio, amino, perfluoroC_{1-6}alkyl, aminocarbonyl, nitro, aminocarbonylC_{2-6}alkenyl, C_{1-6}alkoxyC_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminoC_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkylcarbonylamino, C_{1-6}alkoxycarbonylC_{1-6}alkylcarbonylamino, carboxyC_{1-6}alkylcarbonylamino, aminosulphonyl, carboxyC_{2-6}alkenyl, aminocarbonylC_{1-6}alkylcarbonylamino, C_{1-6}alkylaminocarbonylC_{1-6}alkoxy, phenoxy, carboxyC_{1-6}alkyl, carboxycarbonylamino, thiazolidindionylC_{1-6}alkyl, C_{1-6}alkylcarbonylhydrazocarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, C_{1-6}alkylsulphonylaminoC_{1-6}alkyl, (C_{1-6}alkyloxy)hydroxyphosphinylC_{1-6}alkyl, aminosulphonylC_{1-6}alkyl, C_{1-6}alkoxyaminocarbonylC_{1-6}alkyl, hydroxyaminocarbonylC_{1-6}alkyl, C_{1-6}alkoxyaminocarbonylC_{2-6}alkenyl, aminoC_{1-6}alkyl, and moiety (IV)



(IV)

wherein;

Q is a bond or a bivalent linking group;

Ar represents a carbocyclic or heterocyclic aromatic ring;

R^{12} represents hydrogen or one or more substituent, suitably up to five, independently selected from the list consisting of carboxyC_{2-6}alkenyl, C_{1-6}alkylcarbonylamino, amino, C_{1-6}alkylamino, (di-C_{1-6}alkyl)amino, halo, cyano, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, (di-C_{1-6}alkyl)aminocarbonyl, carboxyC_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, carboxy, hydroxy, aminocarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, C_{1-6}alkylaminocarbonylC_{1-6}alkyl, morpholinylC_{1-6}alkylaminocarbonylC_{1-6}alkyl, C_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxyaminocarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, phenyl, hydroxyC_{1-6}alkyl, morpholinyl, piperidinyl, cyanoC_{1-6}alkyl, (C_{1-6}alkylpiperidinyl)C_{1-6}alkoxy, (C_{1-6}alkylcarbonyl)(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, (di-C_{1-6}alkyl)aminoC_{1-6}alkyl, aminosulphonyl, ureido, and C_{1-6}alkylsulphonylamino.

When Ar is a carbocyclic aromatic ring, examples include phenyl.

When Ar is a heterocyclic aromatic ring, examples include oxazolyl, benzothiazolyl, quinolinyl, oxadiazolyl, pyrimidinyl, pyrazinyl, dihydropyridazinonyl, pyrazolyl, imidazolyl, pyrazinonyl, dihydro-oxadiazinonyl, pyridazinonyl, and pyridinyl.

Examples of Q include -[CONH], -[$(CH_2)_{1-6}O$]-, -[$CONH(CH_2)_{1-6}$]-, -[$(CH_2)_{1-6}CONH(CH_2)_{1-6}$)]-, -[S]-, -[O]-, -[$(CH_2)_{1-6}CONH$]-, -[CO]-, -[$O(CH_2)_{1-6}$]-, -[NHCO]-, -[$NHSO_2$]-, -[$(CH_2)_{1-6}NHCO(CH_2)_{1-6}$]-, -[$SO_2NH$]-, -[$(CH_2)_{1-6}NHSO_2(CH_2)_{1-6}$]-, -[$NHCO(CH_2)_{1-6}$]-, a bond, -[$(CH_2)_{1-6}NHCO$]-, -[$(CH_2)_{1-6}NHSO_2$]-, –[NH]-, -[$CH_2O$]-, -[$(CH_2)_{1-6}SO_2NH$]-, -[$(CH_2)_{1-6}CO_2(CH_2)_{1-6}SO_2$]-, -[$(CH_2)_{1-6}CONHNHCO$]-, -[$(CH_2)_{1-6}CO_2(CH_2)_{1-6}$]-,-[$O(CH_2)_{1-6}N(C_{1-6}alkyl)$]-, -[$S(CH_2)_{1-6}$]-, and -[$SO_2$]-.

Suitable substituents for any alkyl group include cyano, C_{1-6}alkylaminocarbonyl, aminosulphonyl, C_{1-6}alkoxy, C_{1-6}alkylsulphonylamino, hydroxy, carboxy, phenylaminocarbonyl, phenylC_{1-6}alkylaminocarbonyl, phenylcarbonylamino, phenylC_{1-6}alkylcarbonylamino, thiazolidinedionyl, piperazinylcarbonyl where the piperazinyl group may be substituted or unsubstituted, morpholinylcarbonyl, piperidinylcarbonyl, hydroxyC_{1-6}alkylaminocarbonyl, (di-C_{1-6}alkylamino)carbonyl, C_{1-6}alkylaminosulphonyl, aminocarbonyl, (di-C_{1-6}alkylamino)C_{1-6}alkylaminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonylamino, C_{1-6}alkoxyC_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminoC_{1-6}alkylcarbonylamino, C_{1-6}alkoxycarbonylC_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkylcarbonylamino, and (di-C_{1-6}alkylamino)sulphonyl.

Suitable substituents for any piperazinyl group include C_{1-6}alkyl.

Suitably, R^1 is unsubstituted phenyl or phenyl substituted with; 4-[S-(3-CH_2CO_2H)Ph], 4-[S-(3-CONHMe)Ph], 4-[O-(3-CO_2H)Ph], 3-CO_2H, 3-[$CH_2CONHPh$], 4-[$CH_2CONHPh$], 3-COPh, 3-OCH_2Ph, 4-[NHCO-(2-OH)Ph], 3-CO_2Et, 4-[S-(2-CO_2H)Ph], 4-[O-(3-CONHMe)Ph], 4-[O-(3-$CONH_2$)Ph], 4-[S-(3-$CONH_2$)Ph], 4-[O-(4-CONHMe)Ph], 4-[NHCOPh], 4-[S-[3-$CONH(CH_2)_2OMe$]Ph], 4-[S-(2-CO_2H)Ph], 4-[$NHCOCH_2Ph$], 3-[$NHCOCH_2Ph$], 3-CONHPh, 4-[O-(4-CO_2H)Ph], 4-SPh, 4-[$CH_2NHCOCH_2Ph$], 3-CONHMe, 4-[O-(4-$CONH_2$)Ph], 4-[S-(3-$CH_2CONHMe$)Ph], 4-[S-[3-$CH_2CONH(CH_2)_2$(morpholin-4-yl)]Ph], 3-SO_2NHPh, 3-$CH_2NHCOPh$, 4-[$NHSO_2$(4-Me)Ph], 3-$CH_2NHCOCH_2Ph$, 4-[$NHCO(CH_2)_2Ph$], 4-[S-

(3-CH_2CONH_2)Ph], 4-[S-(3-CO_2H)Ph], 4-[S-(3-$CH_2CONHOH$)Ph], 4-[O-(2-CO_2H)Ph], 4-Ph, 4-[S-(2-CH_2CO_2Me)Ph], 4-[S-(4-$CONH_2$)Ph], 4-[S-(4-CO_2H)Ph], 4-[O-(2-CONHMe)Ph], 4-[CH_2CONH-(3-CO_2H)Ph], 4-[O-(3-CH_2CO_2H)Ph], 4-[S-(2-CO_2H)Ph], 4-[O-(2-$CONH_2$)Ph], 3-[CH_2(1,3-thiazolidine-2,4-dion-5-yl)], 3,5-di-F, 3-Cl, 3-OCH_2CO_2H, 3-CONHMe-4-NHMe, 4-[CH_2CO(4-Me-piperazin-1-yl)], 2-[morpholin-4-yl], 3-[CH_2CO(morpholin-4-yl)], 3-[CH_2CO(piperidin-1-yl)], 4-[CH_2CO(piperidin-1-yl], 4-[$CH_2CONH(CH_2)_2OH$], 4-[CH_2CONMe_2], 3-[CONHMe]-4-Cl, 3-$SO_2NH(CH_2)_2OMe$, 3-SO_2NHn-Bu, 3-COMe, 3-CH_2CO_2H, 3-NHCOMe, 4-$NHCOCF_3$, 2-Me, 2-Me-4-F, 2-Me-5-F, 3-Me, 2-SMe, 3-CF_3-4-NH_2, 3-CF_3-4-NHCOMe, 4-CH_2SO_2NHMe, 4-$CH_2CH_2CONH_2$, 4-Me, 3-[$CH_2CONH(CH_2)_2NMe_2$], 4-NH_2, 3-NO_2, 3-NH_2, 2,3,4-tri-F, 3-F-5-CF_3, 4-[$O(CH_2)_3CO_2H$], 4-CH_2NHCO_2t-Bu, trans-4-[CH=CHC(O)NH_2], 4-[$NHCOCH_2OMe$], 4-[$NHCOCH_2NHCOMe$], 4-CH_2NHCOn-Pr, 4-[$NHCOCH_2OH$], 3-[$NHCOCH_2OMe$], 4-[$NHCOCH_2CO_2$t-Bu], 3-[$NHCOCH_2NHC(O)Me$], 4-[NHCOn-Pr], 4-[$NHCOCH_2CO_2H$], 4-[$CH_2NHCOCH_2OMe$], 4-[$CH_2NHCOCH_2NHCOMe$], 4-[$(CH_2)_3CO_2H$], 3-[CH_2NHCO_2t-Bu], 4-[$CH_2NHCOCH_2OH$], 4-[NHCOMe], 3-[$NHCOCH_2OH$], 3-OH-4-[NHCOMe], 4-[$CH_2NHCOCH_2CO_2$t-Bu], 3-[CH_2CONH_2], 3-[SO_2NH_2], 3-[$CH_2NHCOCH_2OMe$], 3-[$CH_2NHCOCH_2NHCOMe$], 3-[$CH_2NHCOCH_2OH$], trans-4-[CH=$CHCO_2H$], 4-[$NHCO(CH_2)_2CONH_2$], 4-$O(CH_2)_3CONHMe$, 4-[NHCOMe], 4-[CH_2SO_2NHMe], 4-[$CH_2SO_2NMe_2$], 3-[CH_2CONH_2], 4-[CH_2SO_2NHMe], 4-[CH_2(1,3-thiazolidine-2,4-dion-5-yl)], 3-[oxazol-5-yl], 4-[$NHCO(CH_2)_2$(3-pyridinyl)], 4-[5-Me-2-oxazolyl], 4-[2-Me-4-oxazolyl], 4-[S-(2-$CONH_2$)Ph], 4-[S-(2-CONHMe)Ph], 4-[CH_2CONH-(4-CO_2H)Ph], 3-[CH_2CONH-(4-CO_2H)Ph], 3-CO_2H-4-[O-Ph], 3-CO_2H-4-[O-(4-Ph)Ph], 3-[CONH-(4-CO_2H)Ph], 3-[CH_2O-(4-CO_2H)Ph], 4-[CH_2SO_2NH-Ph], 4-[O-(4-CO_2H)Ph], 3-[O-(4-CO_2H)Ph], 3-[O-(4-CH_2CO_2H)Ph], 4-[O-(4-CH_2CO_2H)Ph], 3-[CH_2CONH-(4-CH_2CH_2OH)Ph], 3-[O-(3-CO_2H)Ph], 3-[O-(4-$CH_2CH_2CO_2H$)Ph], 3-[CH_2CONH-(4-(morpholin-4-yl)Ph], 3-[CH_2CONH-(4-(piperidin-1-yl)Ph], 3-[CH_2CONH-(4-CH_2OH)Ph], 4-[O-(3-NMe_2)Ph], 3-[OCH_2-(4-CO_2H)Ph], 3-[$CH_2CO_2CH_2CH_2SO_2$-(4-NH_2)Ph], 3-[CH_2CONH-(4-NMe_2)Ph], 3-[CH_2CONH-(3-Cl-4-(morpholin-4-yl)Ph], 3-[CH_2CONH-(4-CH_2CN)Ph], 3-[CH_2CONH-4-(OCH_2(1-methylpiperidin-4-yl)Ph)], 3-[O-(3-NH_2)Ph], 4-[O-4-NHCOMe)Ph], 3-Me-4-[O-(4-CH_2CO_2H)Ph], 4-[CH_2SO_2NH-(4-CO_2H)Ph], 4-[O-(3-NHCOMe)Ph], 3-[CH_2CONH-(3-NHCOMe)Ph], 3-[CH_2CONH-(4-NHCOMe)Ph], 3-[CH_2CONH-(4-N(Me)COMe)Ph], 3-[CH_2CONH-(3-$CONH_2$)Ph], 3-[CH_2CONH-(2-$CONH_2$)Ph], 3-[CH_2CONH-(3-NMe_2)Ph], 4-[CH_2SO_2NH-(4-CH_2CO_2H)Ph], 4-[CH_2SO_2NH-(3-CH_2CO_2H)Ph], 4-[CH_2SO_2NH-(3-CO_2H)Ph], 3-Cl-4-[O-(4-CH_2CO_2H)Ph], 3-Cl-4-[O-(4-CO_2H)Ph], 3-[CH_2CONH-(3-CO_2H)Ph], 3-[$CH_2CONHCH_2$-(4-NMe_2)Ph], 3-[$CH_2CONHNHCO$-(4-NH_2)Ph], 4-[O-(4-$CH_2NHCOMe$)Ph], 3-CO_2H-4-[O-(4-Cl)Ph], 3-[O-(4-NHCOMe)Ph], 3-[CH_2CONH-(4-$CONH_2$)Ph], 4-[O-(3-$NHCONH_2$)Ph], 4-[O-(4-$CH_2CH_2NMe_2$)Ph], 3-[CH_2CONH-(3-NH_2)Ph], 3-[CH_2CONH-(4-NH_2)Ph], 3-[$CH_2CONHNHCO$-Ph], 3-[CH_2CONH-(4-SO_2NH_2)Ph], 3-[CH_2CONH-(3-CH_2OH)Ph], 3-[$CH_2CONH(CH_2)_2$-(4-NH_2)Ph], 3-[$CH_2CONHNHCO$-(3-NH_2)Ph], 3-[CH_2SO_2NH-Ph], 3-[CH_2SO_2NH-(3-CO_2H)Ph], 3-[CH_2CONH-(4-$NHSO_2Me$)Ph], 3-[CH_2SO_2NH-(4-CO_2H)Ph], 3-[SO_2-(3-NH_2)Ph], 4-

[O-(4-SO_2NH_2)Ph], 4-[O-(4-NH_2)Ph], 4-[CH_2SO_2NH-(4-$NHSO_2Me$)Ph], 4-[CH_2SO_2NH-(4-NHCOMe)Ph], 4-[6-Me-2-benzothiazolyl], 4-[O-(3-pyridinyl)], 3-[2-benzothiazolyl], 3-[CH_2CONH(3-quinolinyl)], 4-[3-Me-1,2,4-oxadiazol-5-yl], 3-[CH_2CONH(2-Me-pyridin-3-yl)], 3-[CH_2CONH(5-Me-pyridin-3-yl)], 3-[CH_2CONH(2-OMe-pyridin-5-yl)], 3-[CH_2CONH(pyridin-3-yl)], 3-[$CH_2CO_2CH_2$(3-NH_2-pyridin-2-yl)], 4-[$O(CH_2)_2NMe$(pyridin-2-yl)], 4-[OCH_2(pyridin-3-yl)], 3-[CH_2CONH(pyrimidin-4-yl)], 3-[CH_2CONH(pyrazin-2-yl)], 4-[O-(pyridin-2-yl)], 4-[2-OH-pyrimidin-5-yl)], 4-[5-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl)], 4-[2,5-di-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl)], 4-[1H-pyrazol-3-yl], 4-[SCH_2(1H-imidazol-4-yl)], 3-[CH_2SO_2NH(pyridin-3-yl)], 4-[2-OMe-pyrazin-5-yl)], 4-[1H-pyrazin-2-on-5-yl)], 4-[5,6-dihydro-4H-[1,3,4]-oxadiazin-5-on-2-yl)], 4-[4,5-dihydro-2H-pyridazin-3-on-6-yl)], 4-[2H-pyridazin-3-on-6-yl)], 3-$CH_2CH_2CO_2H$, 4-$CH_2CH_2CH_2CO_2H$, 4-$CH_2CH_2CH_2CO_2H$, 4-OH, 3,5-di-Cl-4-OH, 4-$(CH_2)_2CO_2H$, 3-F-4-OCH_2CO_2H, 4-$NHCOCO_2H$, 3-Me-4-*trans*-$CH=CHCO_2H$, 3-$CH_2CONHNHCOMe$, 4-$(CH_2)4NHCOMe$, 4-$(CH_2)_4NHSO_2Me$, 3-CH_2NHSO_2Me, 4-$CH_2CH_2P(O)(OEt)OH$, 4-$CH_2CH_2SO_2NH_2$, 3-$CH_2SO_2NH_2$, 3-$CH_2CONHOMe$, 3-$CH_2CONHOH$, 4-trans-CH=CHCONHOMe, 4-CH_2NH_2, or 3-CH_2NH_2.

Favourably, R^1 is phenyl substituted with 4-[S-(3-CH_2CO_2H)Ph].

Suitably, R^1 is pyridin-5-yl substituted with 2-[$(CH_2)_3CN$]-3-Me, 2-[$(CH_2)_2CO_2H$]-, 2-[$(CH_2)_4CO_2H$]-, 2-[$(CH_2)_3CN$]-3-CO_2Et, or 2-[OPh].

Suitably, R^1 is pyridin-3-yl substituted with 2-Me, or 2-[$(CH_2)_3CN$].

When R^1 is a substituted or unsubstituted carbocyclic aromatic ring which ring is fused to a substituted or unsubstituted heterocyclic aromatic or non-aromatic ring, suitable substituents for either ring include carboxyC_{1-6}alkylthio and esters thereof, halo, aminocarbonyl, hydroxy, aryloxy, arylthio, arylamino, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylthio, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, carboxy, carboxyC_{1-6}alkyl, substituted or unsubstituted aryl, arylC_{1-6}alkyl, amino, di-(C_{1-6}alkyl)amino, di-(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, di-(C_{1-6}alkyl)aminoC_{1-6}alkylamino, morpholinyl, C_{1-6}alkylcarbonylamino, and C_{1-6}alkylamino.

Suitably, R^1 is indolin-5-yl unsubstituted or substituted with 1-(SO_2Me), or 1-CO_2t-Bu.

Suitably, R^1 is indan-5-yl.

Suitably, R^1 is quinolin-6-yl.

Suitably, R^1 is indol-5-yl unsubstituted or substituted with [1-Me-2-$CONH_2$], 1-Me, or [1-Me-2-CO_2H].

Suitably, R^1 is benzoxazol-5-yl substituted with 2-Me.

Suitably, R^1 is unsubstituted benzoxazol-6-yl, or benzoxazol-6-yl substituted with 2-Me.

Suitably, R^1 is benzothiazol-5-yl substituted with 2-Me.

Suitably, R^1 is unsubstituted benzothiazol-6-yl or benzothiazol-6-yl substituted with 2-[NHCOMe], 2-NH_2, 2-NHiPr, 2-[NHEt], 2-[morpholin-4-yl], 2-[$NH(CH_2)_3N(Me)_2$], 2-[$(CH_2)_4CO_2H$], 2-[$(CH_2)_4CO_2Me$], 2-NHPh, 2-[$S(CH_2)_3CO_2H$], 2-Ph, 2-NHMe, 2-$N(Me)_2$, 2-Cl, 2-SMe, 2-Me, 2-(SCH_2CO_2Me), or 2-(SCH_2CO_2H).

Suitably, R^1 is benzthiazolinon-6-yl unsubstituted or substituted with 3-CH_2CO_2Me, 3-[3-F-Ph], 3-[4-OMe-Ph], 3-[CH_2Ph], 3-[3-NHCOMe-Ph], 3-[$(CH_2)_3N(Me)_2$], 3-Me, 3-CH_2CO_2H.

Suitably, R^1 is benzoxazolinon-6-yl.

Suitably, R^1 is benzoxazolinon-5-yl.

Suitably, R^1 is benzimidazol-5-yl substituted with 2-Me.

Suitably, R^1 is benzimidazolinon-5-yl unsubstituted or substituted with 1,3-di-Me

Suitably, R^1 is benzothiophen-5-yl.

Suitably, R^1 is benzofuran-5-yl substituted with 2-CO_2H.

Suitably, R^1 is indolin-2-on-5-yl.

Suitably, R^1 is 2H-1,4-benzothiazin-3(4H)-on-7-yl.

Favourably, R^1 is unsubstituted benzoxazolinon-6-yl.

Favourably, R^1 is unsubstituted benzthiazolinon-6-yl.

Favourably, R^1 is unsubstituted indolin-2-on-5-yl.

Favourably, R^1 is benzothiazol-6-yl substituted with a 2-amino group.

When R^2 is a substituted carbocyclic or heterocyclic aromatic ring, suitable substituents include up to five groups independently selected from the list consisting of hydroxyC_{1-6}alkyl, carboxy, cyano, aminocarbonyl, halo, C_{1-6}alkoxy, nitro, perfluoroC_{1-6}alkyl, benzoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulphonyl, hydroxy, -$O(CH_2)_wO$- where w is 1 to 4, phenoxy, benzyloxy, C_{1-6}alkoxyC_{1-6}alkyl, perfluoroC_{1-6}alkoxy, C_{1-6}alkylS-, perfluoroC_{1-6}alkylS-, (diC_{1-6}alkyl)N-, amino, C_{1-6}alkylcarbonylamino, substituted or unsubstituted ureido, phenylcarbonylamino, benzylcarbonylamino, styrylcarbonylamino, C_{1-6}alkyl, and phenyl.

Suitable substituents for ureido include fluorophenyl, phenylC_{1-6}alkyl-, cyclohexyl, C_{1-6}alkenyl, C_{1-6}alkyl, and C_{1-6}alkoxyphenyl.

Suitably, R^2 is unsubstituted phenyl or phenyl substituted with 4-NO_2, 4-NHCOMe, 4-I, 2,3-di-F, 3-CN, 2,3,6-tri-F, 3-CO_2H, 3-CH_2OH, 2,3,5-tri-F, 3,5-di-Me, 3-F, 2-Cl-5-F, 2-Cl, 2-F-3-Cl, 2-Cl-3-F, or 4-Cl.

Favourably, R^2 is phenyl substituted with 2,3-di-F.

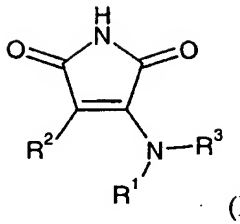
When R^1 and R^3 form substituted indolinyl, suitable substituents include hydroxyC_{1-6}alkyl and C_{1-6}alkoxyC_{1-6}alkyl.

Suitably, R^1 and R^3 form indolinyl substituted with 2-(hydroxymethyl) or 2-(methoxymethyl).

Suitably, R^1 and R^3 form tetrahydroquinolinyl.

Preferred compounds of formula (I) are selected from the list consisting of Example A1 in Table A, and Example B10, Example B16, Example B47, and Example B49 in Table B.

There is a sub-group of compounds, falling wholly within formula (I), and being of formula (I')



(I')

wherein;

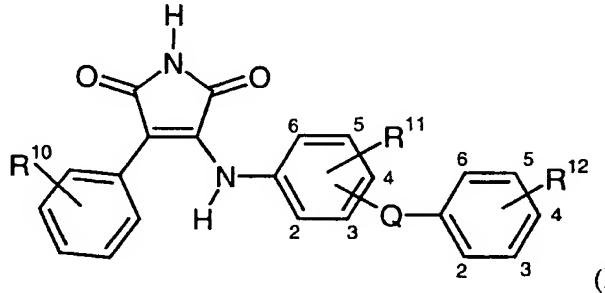
R^1, R^2, and R^3 are as defined in formula (I), with the proviso that formula (I') does not include the following compound:

3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione.

It is considered that the compounds of formula (I') are novel. Accordingly, the present invention also provides a compound of formula (I') or a derivative thereof.

Preferred compounds of formula (I') are selected from the list consisting of Example A1 in Table A, and Example B10, Example B16, Example B47, and Example B49 in Table B.

There is a subgroup of compounds falling wholly within formula (I') being of formula (IA)



(IA)

wherein;

R^{10} represents hydrogen or one or more substituents, suitably up to five, independently selected from the list consisting of halo and cyano;

R^{11} represents hydrogen or one or more substituents, suitably up to four, independently selected from the list consisting of carboxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkylaminocarbonyl, halo, and C_{1-6}alkyl;

Q represents a bond or a bivalent linking group.

Examples of Q include –[CONH]-, -[$(CH_2)_{1-6}O$]-, -[$CONH(CH_2)_{1-6}$]-, -[$(CH_2)_{1-6}CONH(CH_2)_{1-6}$)]-, -[S]-, -[O]-, -[$(CH_2)_{1-6}CONH$]-, -[CO]-, -[$O(CH_2)_{1-6}$]-, -[NHCO]-, -[$NHSO_2$]-, -[$(CH_2)_{1-6}NHCO(CH_2)_{1-6}$]-, -[$SO_2NH$]-, -[$(CH_2)_{1-6}NHSO_2(CH_2)_{1-6}$]-, -[$NHCO(CH_2)_{1-6}$]-, a bond, -[$(CH_2)_{1-6}NHCO$]-, -[$(CH_2)_{1-6}NHSO_2$]-, -[NH]-, -[$(CH_2)_{1-6}SO_2NH$]-, -[$(CH_2)_{1-6}CO_2(CH_2)_{1-6}SO_2$]-, -[$(CH_2)_{1-6}CONHNHCO$]-, and -[$SO_2$]-.

R^{12} represents hydrogen or one or more substituent, suitably up to five, independently selected from the list consisting of C_{1-6}alkylcarbonylamino, amino, C_{1-6}alkylamino, (di-C_{1-6}alkyl)amino, halo, cyano, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, (di-

C_{1-6}alkyl)aminocarbonyl, hydrogen, carboxyC_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, carboxy, hydroxy, aminocarbonyl, C_{1-6}alkoxyC_{1-6}alkylaminocarbonyl, C_{1-6}alkylaminocarbonylC_{1-6}alkyl, morpholinylC_{1-6}alkylaminocarbonylC_{1-6}alkyl, C_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxyaminocarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, phenyl, hydroxyC_{1-6}alkyl, morpholinyl, piperidinyl, cyanoC_{1-6}alkyl, (methylpiperidinyl)C_{1-6}alkoxy, (C_{1-6}alkylcarbonyl)(C_{1-6}alkyl)amino, C_{1-6}alkoxyaminoC_{1-6}alkyl, (di-C_{1-6}alkyl)aminoC_{1-6}alkyl, aminosulphonyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, ureido, and C_{1-6}alkylsulphonylamino.

Suitably, R^{10} represents hydrogen, 2,3-di-F, 3-CN, 2-F-3-Cl, 2,3,6-tri-F, 2-Cl-3-F, and 4-Cl.

Favourably, R^{10} represents 2,3-di-F.

Suitably, R^{11} represents hydrogen, 3-CO_2H, 3-CO_2Et, 3-CONHMe, 3-Me, or 3-Cl.

Suitably, Q represents 4-[S]-, 4-[O]-, 3-[CH_2CONH]-, 4-[CH_2CONH]-, 3-[CO]-, 3-[OCH_2]-, 4-[NHCO]-, 4-[$NHCOCH_2$]-, 3-[$NHCOCH_2$]-, 3-[NHCO]-, 4-[$CH_2NHCOCH_2$]-, 3-[SO_2NH]-, 3-[CH_2NHCO]-, 4-[$NHSO_2$]-, 3-[$CH_2NHCOCH_2$]-, 4-[$NHCOCH_2CH_2$]-, a bond at position 4, 3-[CONH]-, 3-[CH_2O]-, 4-[CH_2SO_2NH]-, 3-[O]-, 3-[$CH_2CONHNHCO$]-, 3-[$CH_2CONH(CH_2)_2$]-, 3-[$CH_2CONHCH_2$]-, 3-[$CH_2CO_2(CH_2)_2SO_2$]-, 3-[SO_2]-, 3-[CH_2SO_2NH]-, or 4-[CH_2SO_2NH]-. The position of the linking moiety Q is defined with respect to the atom numbering depicted in formula (IA).

Favourably, Q represents 4-[S]-.

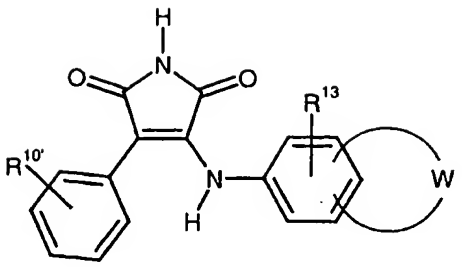
Suitably, R^{12} represents hydrogen, 4-CH_2CO_2H, 4-$CH_2CH_2CO_2H$, 4-CH_2OH, 3-NMe_2, 4-NH_2, 4-NMe_2, (3-Cl-4-morpholin-4-yl), 4-CH_2CN, 4-OCH_2-(1-Me-piperidin-4-yl), 3-CH_2CO_2H, 3-CONHMe, 3-CO_2H, 2-OH, 2-CO_2H, 3-$CONH_2$, 4-CONHMe, 3-[$CONH(CH_2)_2OMe$], 4-CO_2H, 4-$CONH_2$, 3-[$CH_2CONH(CH_2)_2$morpholin-4-yl], 4-Me, 3-CH_2CONH_2, 3-$CH_2CONHOH$, 2-CH_2CO_2Me, 2-CONHMe, 3-$CH_2CONHMe$, 2-$CONH_2$, 4-Ph, 4-CH_2CH_2OH, 4-morpholin-4-yl, 4-piperidin-1-yl, 4-$CH_2NHCOMe$, 3-NH_2, 4-NHCOMe, 3-NHCOMe, 4-N(Me)COMe, 4-$CH_2NHCOMe$, 4-Cl, 3-$NHCONH_2$, 4-$CH_2NHCOMe$, 4-$CH_2CH_2NMe_2$, 4-SO_2NH_2,3-CH_2OH, or 4-$NHSO_2Me$.

Favourably, R^{12} represents 3-CH_2CO_2H.

Preferably, a compound of formula (IA) is Example A1 of Table A.

It is considered that the compounds of formula (IA) are novel. Accordingly, the present invention also provides a compound of formula (IA) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I') being of formula (IB)



(IB)

wherein;

$R^{10'}$ represents hydrogen or one or more substituents, suitably up to five, selected from the list consisting of cyano, halo, carboxy, and hydroxyC_{1-6}alkyl;

R^{13} represents hydrogen;

W represents -[S-CH=N]-, -[$(CH_2)_{2-4}N(SO_2C_{1-6}$alkyl)]-, -[$(CH_2)_{3-5}$]-, -[N=C($C_{1-6}$alkyl)-S]-, -[S-C($C_{1-6}$alkyl)=N]-, -[O-C($C_{1-6}$alkyl)=N]-, -[N=C($C_{1-6}$alkyl)-O]-, -[O-CH=N]-, -[CH=CH-N(C_{1-6}alkyl)]-, -[O-CO-NH]-, -[S-C(S$(CH_2)_{1-6}CO_2C_{1-6}$alkyl)=N]-, -[S-C(S$(CH_2)_{1-6}CO_2H$)=N]-, -[CH=CH-CH=N]-, –[S-CO-NH]-, -[N(C_{1-6}alkyl)-CH=N], -[S-C(halo)=N], -[S-C(SC_{1-6}alkyl)=N], -[NHCONH], -[S-C(Ph)=N], -[S-C(NHC_{1-6}alkyl)=N], -[S-C(N(C_{1-6}alkyl)$_2$)=N], -[S-C(=O)N($(CH_2)_{1-6}CO_2C_{1-6}$alkyl)], -[S-C(=O)N($(CH_2)_{1-6}CO_2H$)], -[CH=CH-S], -[S$(CH_2)_{1-6}CO_2H$]=N], -[S-C(NHPh)=N], -[N(C_{1-6}alkyl)CON(C_{1-6}alkyl)], -[S-CO-N(C_{1-6}alkyl)], -[S-C[$(CH_2)_{1-6}CO_2C_{1-6}$alkyl]=N], -[S-C[$(CH_2)_{1-6}CO_2H$]=N], -[CH=C(CO_2H)-O], -[S-C[NH$(CH_2)_{1-6}$N(C_{1-6}alkyl)$_2$]=N], -[S-CO-N[$(CH_2)_{1-6}$N(C_{1-6}alkyl)$_2$], -[S-C(Morpholin-4-yl)=N], -[S-CO-N(unsubstituted or substituted Ph)], -[S-CO-N($(CH_2)_{1-6}$Ph)], -[CH=C(CO_2H)-N(C_{1-6}alkyl)], -[$(CH_2)_{2-4}N(CO_2C_{1-6}$alkyl)], -[$(CH_2)_{2-4}$NH], -[$(CH_2)_{1-3}$CONH], -[S-C(NH$C_{1-6}$alkyl)=N], -[S-C($NH_2$)=N], [NH-CO-O], -[CH=C($CONH_2$)-N($C_{1-6}$alkyl)], -[O$(CH_2)_{1-2}$CONH], or -[S-C(NHCO$C_{1-6}$alkyl)=N].

Suitably, $R^{10'}$ represents hydrogen, 3-CN, 2,3-di-F, 2,3,6-tri-F, 3-CO_2H, 2-F-3-Cl, 2-Cl-3-F, or 3-CH_2OH.

Favourably, $R^{10'}$ represents 2,3-di-F.

Suitably, R^{13} represents hydrogen.

Suitably, W represents 3,4-[S-CH=N]-, 3,4-[$CH_2CH_2N(SO_2Me)$]-, 3,4-[$CH_2CH_2CH_2$]-, 3,4-[N=C(Me)-S]-, 3,4-[S-C(Me)=N]-, 3,4-[O-C(Me)=N]-, 3,4-[N=C(Me)-O]-, 3,4-[O-CH=N]-, 3,4-[CH=CH-N(Me)]-, 3,4-[O-C(O)-NH]-, 3,4-[S-C(SCH_2CO_2Me)=N]-, 3,4-[S-C(SCH_2CO_2H)=N]-, 3,4-[CH=CH-CH=N]-, 3,4-[S-C(O)-NH]-, 3,4-[N(Me)-CH=N], 3,4-[S-C(Cl)=N], 3,4-[S-C(SMe)=N], 3,4-[NHCONH], 3,4-[S-C(Ph)=N], 3,4-[S-C(NHMe)=N], 3,4-[S-C(NMe_2)=N], 3,4-[S-C(=O)N(CH_2CO_2Me)], 3,4-[S-C(=O)N(CH_2CO_2H)], 3,4-[CH=CH-S], 3,4-[S-C[S$(CH_2)_3CO_2H$]=N], 3,4-[S-C(NHPh)=N], 3,4-[N(Me)CON(Me)], 3,4-[S-CO-N(Me)], 3,4-[S-C[$(CH_2)_4CO_2Me$]=N], 3,4-[S-C[$(CH_2)_4CO_2H$]=N], 3,4-[CH=C(CO_2H)-O], 3,4-[S-C[NH$(CH_2)_3NMe_2$]=N], 3,4-[S-CO-N[$(CH_2)_3NMe_2$]], 3,4-[S-C(Morpholin-4-yl)=N], 3,4-[S-CO-N(3-F-Ph)], 3,4-[S-CO-N(4-OMe-Ph)], 3,4-[S-CO-N(CH_2Ph)], 3,4-[S-CO-N(3-NHCOMe-Ph], 3,4-[CH=C(CO_2H)-N(Me)], 3,4-[$CH_2CH_2N(CO_2t$-Bu)], 3,4-[CH_2CH_2NH], 3,4-[CH_2CONH], 3,4-[S-C(NHEt)=N], 3,4-[S-C(NH_2)=N]-, 3,4-[S-

C(NHi-Pr)=N], 3,4-[NH-CO-O], 3,4-[CH=C($CONH_2$)-N(Me)], 3,4-[OCH_2CONH], or 3,4-[S-C(NHCOMe)=N].

Favourably, W represents 3,4-[S-C(NH_2)=N]-.

Favourably, W represents 3,4-[CH_2CONH]-.

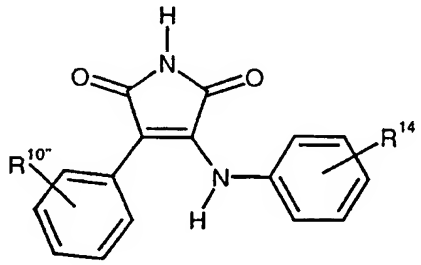
Favourably, W represents 3,4-[O-C(O)-NH]-.

Favourably, W represents 3,4-[S-C(O)-NH]-.

Preferably, a compound of formula (IB) is selected from the list consisting of Examples B10, B16, B47, and B49 of Table B.

It is considered that the compounds of formula (IB) are novel. Accordingly, the present invention also provides a compound of formula (IB) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I) being of formula (IC)



(IC)

wherein;

$R^{10"}$ represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of halo, C_{1-6}alkyl, cyano, carboxy, nitro, C_{1-6}alkylcarbonylamino, and hydroxyC_{1-6}alkyl;

R^{14} represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of carboxycarbonylamino, unsubstituted or substituted C_{1-6}alkyl, halo, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylamino, morpholinyl, C_{1-6}alkoxyC_{1-6}alkylaminosulphonyl, C_{1-6}alkylaminosulphonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonylamino, (perfluoroC_{1-6}alkyl)carbonylamino, C_{1-6}alkylthio, amino, nitro, perfluoroC_{1-6}alkyl, aminocarbonylC_{2-6}alkenyl, C_{1-6}alkoxyC_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminoC_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkylcarbonylamino, C_{1-6}alkoxycarbonylC_{1-6}alkylcarbonylamino, carboxyC_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkylcarbonylamino, hydroxy, aminosulphonyl, carboxyC_{2-6}alkenyl, aminocarbonylC_{1-6}alkylcarbonylamino, carboxyC_{1-6}alkyl, thiazolidindionylC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, C_{1-6}alkylsulphonylaminoC_{1-6}alkyl, (C_{1-6}alkoxy)hydroxyphosphinylC_{1-6}alkyl, aminosulphonylC_{1-6}alkyl, C_{1-6}alkoxyaminocarbonylC_{1-6}alkyl, hydroxyaminocarbonylC_{1-6}alkyl, C_{1-6}alkoxyaminocarbonylC_{2-6}alkenyl, aminoC_{1-6}alkyl, and C_{1-6}alkylaminocarbonylC_{1-6}alkoxy.

Suitable substituents for C_{1-6}alkyl include C_{1-6}alkylcarbonylhydrazocarbonyl, thiazolidindionyl, (piperazinyl)carbonyl wherein the piperazinyl moiety may be unsubstituted or substituted, (morpholinyl)carbonyl, (piperidinyl)carbonyl, hydroxyC_{1-}

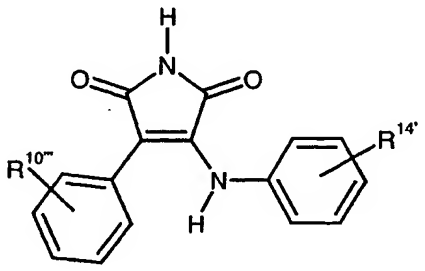
$_{6}$alkylaminocarbonyl, (di-C_{1-6}alkylamino)carbonyl, carboxy, C_{1-6}alkylaminosulphonyl, aminocarbonyl, (di-C_{1-6}alkylamino)C_{1-6}alkylaminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonylamino, C_{1-6}alkoxyC_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminoC_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkylcarbonylamino, C_{1-6}alkoxycarbonylC_{1-6}alkylcarbonylamino, C_{1-6}alkoxyC_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkylcarbonylamino, C_{1-6}alkylaminosulphonyl, and (di-C_{1-6}alkylamino)sulphonyl.

Suitable substituents for piperazinyl include C_{1-6}alkyl.

Suitably, $R^{10"}$ represents hydrogen, 2-F-3-Cl, 2-Cl-3-F, 4-NO_2, 4-I, 2-Cl, 4-NHCOMe, 2,3,5-tri-F, 3,5-di-Me, 2,3,6-tri-F, 2,3-di-F, 3-CN, 3-F, 2-Cl-5-F, 3-CO_2H, or 3-CH_2OH.

Suitably, R^{14} represents hydrogen, 3-[CH_2-(1,3-thiazolidine-2,4-dion-5-yl)], 3,5-di-F, 3-Cl, 3-OCH_2CO_2H, 3-CONHMe-4-NHMe, 4-[CH_2CO(4-Me-piperazin-1-yl)], 2-(morpholin-4-yl), 3-[CH_2CO(morpholin-4-yl)], 3-[CH_2CO(piperidin-1-yl)], 4-[CH_2CO(piperidin-1-yl)], 4-[$CH_2CONH(CH_2)_2OH$], 4-[CH_2CONMe_2], 3-CONHMe-4-Cl, 3-$SO_2NH(CH_2)_2OMe$, 3-SO_2NH*n*Bu, 3-COMe, 3-CH_2CO_2H, 3-NHCOMe, 4-$NHCOCF_3$, 2-Me, 2-Me-4-F, 2-Me-5-F, 3-Me, 2-SMe, 3-CF_3-4-NH_2, 3-CF_3-4-NHCOMe, 4-CH_2SO_2NHMe, 4-$CH_2CH_2CONH_2$, 4-Me, 3-[$CH_2CONH(CH_2)_2NMe_2$], 4-NH_2, 3-NO_2, 3-Cl, 3-NH_2, 2,3,4-tri-F, 3-F-5-CF_3, 4-$O(CH_2)_3CO_2H$, 4-CH_2NHCO_2*t*Bu, 4-*trans*-CH=$CHCONH_2$, 4-$NHCOCH_2OMe$, 4-$NHCOCH_2NHCOMe$, 4-CH_2NHCO*n*Pr, 4-$NHCOCH_2OH$, 3-$NHCOCH_2OMe$, 4-$NHCOCH_2CO_2$*t*Bu, 3-$NHCOCH_2NHCOMe$, 4-NHCO*n*Pr, 4-$NHCOCH_2CO_2H$, 4-$CH_2NHCOCH_2OMe$, 4-$CH_2NHCOCH_2NHCOMe$, 4-$(CH_2)_3CO_2H$, 4-$(CH_2)_3CO_2H$, 3-CH_2NHCO_2*t*Bu, 4-$CH_2NHCOCH_2OH$, 4-NHCOMe, 3-$NHCOCH_2OH$, 3-OH-4-NHCOMe, 4-$CH_2NHCOCH_2CO_2$*t*Bu, 3-CH_2CONH_2, 3-SO_2NH_2, 3-$CH_2NHCOCH_2OMe$, 3-$CH_2NHCOCH_2NHCOMe$, 3-$CH_2NHCOCH_2OH$, 4-*trans*-CH=$CHCO_2H$, 4-$NHCO(CH_2)_2CONH_2$, 4-$O(CH_2)_3CONHMe$, 4-$CH_2SO_2NMe_2$, 4-[CH_2-(1,3-thiazolidine-2,4-dion-5-yl)], 3-$CH_2CH_2CO_2H$, 4-$CH_2CH_2CH_2CO_2H$, 4-OH, 3,5-di-Cl-4-OH, 4-$(CH_2)_2CO_2H$, 3-F-4-OCH_2CO_2H, 4-$NHCOCO_2H$, 3-Me-4-*trans*-CH=$CHCO_2H$, 3-$CH_2CONHNHCOMe$, 4-$(CH_2)_4NHCOMe$, 4-$(CH_2)_4NHSO_2Me$, 3-CH_2NHSO_2Me, 4-$CH_2CH_2P(O)(OEt)OH$, 4-$CH_2CH_2SO_2NH_2$, 3-$CH_2SO_2NH_2$, 3-$CH_2CONHOMe$, 3-$CH_2CONHOH$, 4-trans-CH=CHCONHOMe, 4-CH_2NH_2, or 3-CH_2NH_2.

There is a sub-group of compounds falling wholly within formula (I') and being of formula (IC')



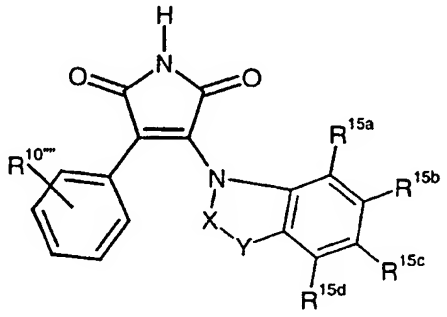
(IC')

wherein;

$R^{10'''}$ and $R^{14'}$ are as defined for $R^{10''}$ and R^{14} respectively in formula (IC), with the proviso that formula (IC') does not include 3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione.

It is considered that compounds of formula (IC') are novel. Accordingly, the present invention also provides a compound of formula (IC') or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I') being of formula (ID)



(ID)

wherein;

$R^{10''''}$ represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of halo and C_{1-6}alkyl;

X-Y represents -[CH((CH$_2$)$_{1-6}$OH)-(CH$_2$)$_{1-4}$]-, -[CH$_2$]$_{1-4}$-, or -[CH((CH$_2$)$_{1-6}$(OC$_{1-6}$alkyl))-(CH$_2$)$_{1-4}$]-;

R^{15a} represents hydrogen;

R^{15b} represents hydrogen;

R^{15c} represents hydrogen;

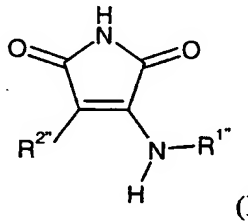
R^{15d} represents hydrogen.

Suitably, $R^{10''''}$ represents hydrogen, 2,3-di-F, 2,3,6-tri-F, 3,5-di-Me, or 2-Cl.

Suitably, X-Y represents –[CH(CH$_2$OH)CH$_2$]-, -[(CH$_2$)$_2$]-, -[(CH$_2$)$_3$]-, or –[CH(CH$_2$OMe)CH$_2$]-.

It is considered that compounds of formula (ID) are novel. Accordingly, the present invention also provides a compound of formula (ID) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I') being of formula (IE)



(IE)

wherein;

$R^{1"}$ is substituted pyridinyl;

$R^{2"}$ is substituted phenyl;

Suitable substituents for pyridinyl include aryloxy, C_{1-6}alkyl, cyanoC_{1-6}alkyl, carboxyC_{1-6}alkyl, or C_{1-6}alkoxycarbonyl.

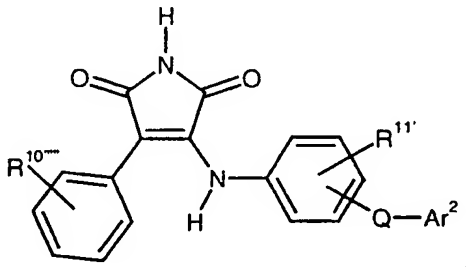
Suitable substituents for phenyl include halo.

Suitably, $R^{1"}$ is 2-[$(CH_2)_3CN$]-3-Me-pyridin-5-yl, 2-Me-pyridin-3-yl, 2-[$(CH_2)_2CO_2H$]-pyridin-5-yl, 2-[$(CH_2)_3CN$]-3-(CO_2Et)-pyridin-5-yl, 2-[$(CH_2)_4CO_2H$]-pyridin-5-yl, 2-OPh-pyridin-5-yl, or 2-[$(CH_2)_3CN$]-pyridin-3-yl.

Suitably, $R^{2"}$ is 2,3-difluorophenyl.

It is considered that compounds of formula (IE) are novel. Accordingly, the present invention also provides a compound of formula (IE) or a derivative thereof.

There is a subgroup of compounds falling wholly within formula (I') being of formula (IF)



(IF)

wherein;

$R^{10''''}$ represents hydrogen or one or more, suitably up to five, substituents selected from the list consisting of halo;

$R^{11'}$ represents hydrogen or hydroxy;

Q represents a bond, -[O]-, -[$(CH_2)_{1-6}CONH$]-, -[$(CH_2)_{1-6}CO_2(CH_2)_{1-6}$]-, -[$O(CH_2)_{1-6}N(C_{1-6}alkyl)$]-, -[$O(CH_2)_{1-6}$]-, -[$S(CH_2)_{1-6}$]-, -[$(CH_2)_{1-6}SO_2NH$]-, or -[$NHCO(CH_2)_{1-6}$]-;

Ar^2 represents oxazolyl, benzothiazolyl, quinolinyl, oxadiazolyl, pyrimidinyl, pyrazinyl, dihydropyridazinonyl, pyrazolyl, imidazolyl, pyrazinonyl, dihydro-oxadiazinonyl, pyridazinonyl, and pyridinyl.

Suitable substituents for oxazolyl include C_{1-6}alkyl.

Suitable substituents for benzothiazolyl include C_{1-6}alkyl.

Suitable substituents for oxadiazolyl include C_{1-6}alkyl.

Suitable substituents for pyrimidinyl include hydroxy.

Suitable substituents for dihydropyridazinonyl include C_{1-6}alkyl.

Suitable substituents for pyrazinyl include C_{1-6}alkoxy.

Suitable substituents for pyridinyl include $C1_{1-6}$alkyl, C_{1-6}alkoxy, and amino.

Suitably, $R^{10''''}$ represents 2,3-di-F.

Suitably, Q represents a bond at position 3, 4-[$NHCO(CH_2)_2$]-, 4-[O], 3-[bond], 3-[CH_2CONH], 3-[$CH_2CO_2CH_2$], 4-[$O(CH_2)_2NMe$], 4-[OCH_2], 4-[SCH_2], 3-

$[CH_2SO_2NH]$, or a bond at position 4. The position of the linking moiety Q is defined with respect to the atom numbering depicted in formula (IF).

Suitably, Ar^2 represents 5-oxazolyl, 3-pyridinyl, 5-Me-2-oxazolyl, 2-Me-4-oxazolyl, 6-Me-benzothiazol-2-yl, 3-pyridinyl, benzothiazol-2-yl, quinolin-3-yl, 3-Me-1,2,4-oxadiazol-5-yl, 2-Me-pyridin-3-yl, 5-Me-pyridin-3-yl, 2-OMe-pyridin-5-yl, 3-NH_2-pyridin-2-yl, pyridin-2-yl, pyrimidin-4-yl, pyrazin-2-yl, 2-OH-pyrimidin-5-yl, 5-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl, 2,5-di-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl, 1H-pyrazol-3-yl, 1H-imidazol-4-yl, 2-OMe-pyrazin-5-yl, 1H-pyrazin-2-on-5-yl, 5,6-dihydro-4H-[1,3,4]-oxadiazin-5-on-2-yl], 4,5-dihydro-2H-pyridazin-3-on-6-yl, or 2H-pyridazin-3-on-6-yl.

It is considered that compounds of formula (IF) are novel. Accordingly, the present invention also provides a compound of formula (IF) or a derivative thereof.

Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including geometric isomers, tautomers, and racemic modifications.

Alkyl groups referred to herein, including those forming part of other groups, include straight or branched chain alkyl groups containing up to twelve, suitably up to six carbon atoms. These alkyl groups may be optionally substituted with up to five, suitably up to three, groups selected from the list consisting of aryl, heterocyclyl, alkylthio, alkenylthio, alkynylthio, arylthio, heterocyclylthio, alkoxy, arylalkoxy, arylalkylthio, amino, mono- or di-alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, phosphonic acid and esters thereof, mono- or dialkylaminosulphonyl, aminosulphonyl, cyano, alkylcarbonylamino, arylcarbonylamino, arylaminocarbonyl, arylalkylaminocarbonyl, arylalkylcarbonylamino, thiazolidinedionyl, piperazinylcarbonyl wherein the piperazine may be unsubstituted or substituted, morpholinylcarbonyl, piperidinylcarbonyl, hydroxyalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyl, dialkylaminoalkylaminocarbonyl, alkoxycarbonylamino, alkoxyalkylcarbonylamino, alkylcarbonylaminoalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylaminocarbonyl, aminosulphonyl, arylsulphonylamino, alkylsulphonylamino, hydroxy, morpholinylalkylaminocarbonyl, hydroxyaminocarbonyl, and halogen.

Alkenyl and alkynyl groups referred to herein include straight and branched chain groups containing from two to twelve, suitably from two to six, carbon atoms. These alkenyl and alkynyl groups may be optionally substituted with up to five, suitably up to three, groups including those substituents described hereinbefore for the alkyl groups.

As used herein the term "carbocyclic" includes aromatic carbocyclic rings, for example aryl groups, and non-aromatic carbocyclic groups, for example cycloalkyl and cycloalkenyl groups, and fused carbocyclic ring systems wherein the carbocyclic rings may be aromatic or non-aromatic, for example indanyl.

Cycloalkyl and cycloalkenyl groups referred to herein include groups having between three and eight ring carbon atoms. These cycloalkyl and cycloalkenyl groups may be optionally substituted with up to five, suitably up to three, groups including those substituents hereinbefore described for the alkyl groups.

As used herein, the term "aryl" includes phenyl, naphthyl, and biphenyl groups, especially phenyl.

Suitably optional substituents for any aryl group include up to five substituents selected from the list consisting of alkylbenzothiazolyl, pyridinyloxy, benzothiazolyl, quinolinylaminocarbonylalkyl, alkyloxadiazolyl, (alkyl)pyridinylaminocarbonylalkyl, (alkoxy)pyridinylaminocarbonylalkyl, pyridinylaminocarbonylalkyl, (amino)pyridinylalkoxycarbonylalkyl, (pyridinyl)(alkyl)aminoalkoxy, pyridinylalkoxy, pyrimidinylaminocarbonylalkyl, pyrazinylaminocarbonylalkyl, hydroxypyrimidinyl, mono or dialkyldihydro-2H-pyridazinonyl, 1H-pyrazolyl, 1H-imidazolylalkylthio, pyridinylaminosulphonylalkyl, alkoxypyrazinyl, pyrazinonyl, dihydro-4H-oxadiazinonyl, dihydro-2H-pyridazinonyl, 2H-pyridazinonyl, aryl, hydroxyalkyl, morpholinyl, piperidinyl, cyanoalkyl, (alkylpiperidinyl)alkoxy, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (dialkyl)aminoalkyl, aminosulphonyl, alkylsulphonylamino, carboxyalkyl, carboxyalkoxy, (thiazolidindionyl)alkyl, alperhaloalkyl, arylaminocarbonyl, aralkyaminocarbonyl, hydroxyalkylaminocarbonyl, arylamino, aminosulphonyl, alkylsulphonylamino, mono- and di-alkylamino, mono- and di-alkylaminocarbonyl, arylaminocarbonylalkyl, arylcarbonyl, aralkoxy, arylcarbonylamino, alkoxyalkylaminocarbonyl, aralkylcarbonylamino, aralkylcarbonylaminoalkyl, aminocarbonyl, morpholinylalkylaminocarbonylalkyl, arylaminosulphonyl, arylcarbonylaminoalkyl, arylsulphonylamino, aminocarbonylalkyl, hydroxyaminocarbonylalkyl, aryl, alkylaminocarbonyl, thiazolidinedionylalkyl, carboxyalkoxy, (alkylpiperazinyl)carbonylalkyl, morpholinyl, morpholinylcarbonylalkyl, piperidinylcarbonylalkyl, hydroxyalkylaminocarbonylalkyl, mono- and di-alkylaminocarbonylalkyl, alkoxyalkylaminosulphonyl, alkoxyamino, perhaloalkylcarbonylamino, alkylaminosulphonylalkyl, mono- and di-alkylaminoalkylaminocarbonylalkyl, carboxyalkoxy, alkoxycarbonylaminoalkyl, aminocarbonylalkenyl, alkoxyalkylcarbonylamino, alkylcarbonylaminoalkylcarbonylamino, alkylcarbonylaminoalkyl, hydroxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, carboxyalkylcarbonylamino, alkoxyalkylcarbonylaminoalkyl, alkylcarbonylaminoalkylcarbonylaminoalkyl, hydroxyalkylcarbonylaminoalkyl, carboxyalkenyl, aminocarbonylalkylcarbonylamino, alkylaminocarbonylalkoxy, alkylaminosulphonylalkyl, aminocarbonylalkyl, oxazolyl, pyridinylalkylcarbonylamino, alkyloxazolyl, alkylthio, alkylaminocarbonylalkyl, halo, alkyl, alkenyl, substituted alkenyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkyloxy, hydroxy, hydroxyalkyl, nitro, amino, cyano, cyanoalkyl , mono- and di-N-alkylamino, acyl, acylamino, N-alkylacylamino, acyloxy, carboxy, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkenyl, ketoalkylester, carbamoyl, carbamoylalkyl, mono- and di-N-alkylcarbamoyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy, arylthio, aralkyloxy, aryloxycarbonyl, ureido, guanidino, morpholino, adamantyl, oxazolyl, aminosulphonyl, alkylaminosulphonyl, alkylthio, haloalkylthio, alkylsulphinyl, alkylsulphonyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, alkoxycarbonyl, trityl, substituted trityl, mono- or bis-alkylphosphonate or mono- or bis-alkylphosphonateC_{1-6}alkyl or any two adjacent

substituents on the phenyl ring together with the carbon atoms to which they are attached form a carbocyclic ring or a heterocyclic ring.

As used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur. Each ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. These heterocyclyl and heterocyclic rings may be unsubstituted or substituted by up to five substituents. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Examples of heterocyclyl and heterocyclic rings include pyridyl, indolinyl, quinolinyl, indolyl, benzoxazolyl, benzothiazolyl, benzothiazolinonyl, benzimidazolinonyl, benzothiophenyl, benzofuranyl, indolinonyl, benzoxazinonyl, quinolinyl, oxadiazolyl, pyrimidinyl, pyrazinyl, dihydropyridazinonyl, pyrazolyl, imidazolyl, pyrazinonyl, dihydro-oxadiazinonyl, pyridazinonyl, benzoxazolinonyl, is benzimidazolyl, benzimidazolinonyl, benzothiophenyl, benzofuranyl, indolinonyl, 2H-benzothiazin-3(4H)-onyl, and benzoxazolinonyl.

Substituents for any heterocyclyl or heterocyclic group are suitably selected from aryloxy, cyano, carboxyalkoxy, morpholinyl, hydroxyalkylaminocarbonyl, alkoxyalkylaminosulphonyl, alkylaminosulphonyl, arylcarbonylamino, aralkylcarbonylamino, aralkenylcarbonylamino, perhalocarbonylamino, perhaloalkyl, aminocarbonyl, nitro, aminocarbonylalkenyl, alkoxyalkylcarbonylamino, alkylcarbonylaminoalkylcarbonylamino, hydroxyalkylcarbonylamino, carboxyalkenyl, aminocarbonylalkylcarbonylamino, alkylaminocarbonylalkoxy, aryl, arylcarbonyl, alkylenedioxy, aryloxy, aralkyloxy, perhaloalkylthio, alkylcarbonyl, alkoxycarbonylalkylthio, carboxyalkylthio, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonyl, halogen, alkyl, arylalkyl, alkoxy, alkoxyalkyl, haloalkyl, hydroxy, amino, mono- and di-N-alkylamino, acylamino, carboxy and salts and esters thereof, carbamoyl, mono- and di-N-alkylaminocarbonyl, aryloxycarbonyl, alkoxycarbonylalkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, alkylthio, alkylsulphinyl, alkylsulphonyl, heterocyclyl and heterocyclylalkyl.

As used herein the terms "halogen" or 'halo' include iodo, bromo, chloro or fluoro, especially chloro or fluoro.

Suitable derivatives of the compounds of the invention are pharmaceutically acceptable derivatives.

Suitable derivatives of the compounds of the invention include salts and solvates.

Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-

bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable pharmaceutically acceptable salts also includes pharmaceutically acceptable acid addition salts, such as those provided by pharmaceutically acceptable inorganic acids or organic acids.

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable inorganic acids includes the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and hydroiodide.

Suitable pharmaceutically acceptable acid addition salts provided by pharmaceutically acceptable organic acids includes the acetate, tartrate, maleate, fumarate, malonate, citrate, succinate, lactate, oxalate, benzoate, ascorbate, methanesulphonate, α-keto glutarate and α-glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

For the avoidance of doubt when used herein the term "diabetes " includes diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

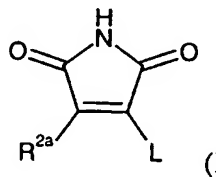
The term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

The term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

The term 'conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

The term 'complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

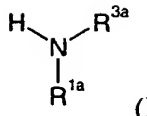
A further aspect of the invention provides a process for the preparation of a compound of formula (I'), which process comprises reaction of a compound of formula (II)



(II)

wherein;

R^{2a} is as defined for R^2 in formula (I) and L is a leaving group, with a compound of formula (III)



(III)

wherein;

R^{1a} and R^{3a} are as defined for R^1 and R^3 respectively in formula (I), and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I') to a further compound of formula (I');

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

Examples of suitable leaving groups, L, are chloro, bromo, triflate, and hydroxy.

The reaction between the compounds of formulae (II) and (III) is carried out in any suitable solvent, for example 1-methyl-2-pyrrolidinone, tetrahydrofuran, or methanol, under conventional amination conditions at any temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time.

Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. When the compound of formula (III) is a weak nucleophile, then the reaction may be assisted by, for example, using temperatures at the upper end of this range, generating the anion of the compound of formula (III) *in situ* using, for example, sodium hydride, or by using a basic catalyst such as triethylamine. Conventional methods of heating also include the use of microwave heating devices, for example a microwave reactor, such as a 100 watt reactor.

The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the residue acidified and the products extracted using solvent extraction, suitably using an organic solvent.

The reaction products are purified by conventional methods, such as chromatography and trituration.

Crystalline product may be obtained by standard methods.

In a preferred aspect, a solution of the compound of formula (II) and a compound of formula (III) in methanol is heated to reflux from between 1 to 4 days, then cooled and concentrated. The residue is then acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extracts are then washed with water, brine, dried with anhydrous magnesium sulphate, and the solvent is removed. The product is then purified by standard methods such as trituration or chromatography, on silica gel, to afford the desired compound.

In a further preferred aspect, a solution of the compound of formula (II) and a compound of formula (III) in 1-methyl-2-pyrrolidinone is heated at 69°C from between 1 to 4 days, then cooled and concentrated. The residue is then acidified with hydrochloric acid, and extracted with ethyl acetate. The organic extracts are then washed with water, brine, dried with anhydrous magnesium sulphate, and the solvent is removed. The

product is then purified by standard methods such as trituration or chromatography, on silica gel, to afford the desired compound.

The above mentioned conversion of a compound of formula (I') into another compound of formula (I') includes any conversion which may be effected using conventional procedures, but in particular the said conversions include any combination of:

(i) for a compound of formula (IA), converting one group R^{11} into another group R^{11};

(ii) for a compound of formula (IA), converting one group R^{12} into another group R^{12}, and;

(iii) for a compound of formula (IC'), converting one group R^{14} into another group R^{14}.

The above mentioned conversions (i) to (iii) may be carried out using any appropriate method under conditions determined by the particular groups chosen.

For a compound of formula (IA);

suitable conversions of one group R^{11} into another group R^{11}, as in conversion (i), include converting a group R^{11} which represents carboxy into a group R^{11} which represents alkylaminocarbonyl; such conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with an amine in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Suitable conversions of one group R^{12} into another group R^{12}, as in conversion (ii), include:

(a). converting a group R^{12} which contains a carboxy group into a group R^{12} which contains an alkylaminocarbonyl group; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with an amine in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

(b). converting a group R^{12} which contains a carboxy group into a group R^{12} which contains an aminocarbonyl group; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with the ammonium salt of N-hydroxysuccinimide in the presence of a suitable activating agent such as 1,3-dicyclohexylcarbodiimide.

(c). converting a group R^{12} which contains a carboxy group into a group R^{12} which contains a hydroxyaminocarbonyl group; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with O-(t-butyldimethylsilyl)hydroxylamine in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

For a compound of formula (IC');

suitable conversions of one group R^{14} into another group R^{14}, as in conversion (iii), include:

(a). converting a group R^{14} which represents nitro into a group R^{14} which represents amino; such a conversion may be carried out using a conventional reduction procedure, for example hydrogenating an appropriately protected compound of formula (I).

(b). converting a group R^{14} which represents amino into a group R^{14} which represents acylamino; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with a carboxylic acid in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

(c). converting a group R^{14} which represents aminoalkyl into a group R^{14} which represents acylaminoalkyl; such a conversion may be carried out using a conventional procedure for the formation of amide bonds, for example treating an appropriately protected compound of formula (I) with a carboxylic acid in the presence of suitable activating agents such as a mixture of 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional procedures.

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The derivatives of the compounds of formula (I), including salts and/or solvates, may be prepared and isolated according to conventional procedures.

The compounds of formula (II) are known compounds or they may be prepared using methods analogous to those used to prepare compounds such as those described in International Patent Application, Publication Number WO97/34890 and Wiley, R.H. and Slaymaker, S.C. J. Am. Chem. Soc. (80) 1385 (1958). The compounds of formula (II) may be inter-converted in an analogous manner to the above mentioned inter-conversions of the compounds of formula (I).

The compounds of formula (III) are either commercially available, or are reported in the chemical literature, or are prepared by analogy with known conventional literature procedures, for example those disclosed in *J. Org. Chem* 1998, 63, 6338, *Tet. Lett.* 1984, 25, 3383, *Synlett.* 1997, 133, *Synth. Commun.* 1995, 25, 1077, *Bioorg. Med. Chem. Lett.* 1997, 7, 1345, *Synthesis* 1994, 1413, and *Chem. Pharm. Bull.* 1982, 30, 3580, *J. Het. Chem.* 1992, 29, 1069, or in standard reference texts of synthetic methodology such as J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

3-Phenylamino-4-phenyl-1H-pyrrole-2,5-dione may be prepared according to procedures disclosed in *J. Amer. Chem. Soc.* 1958, 80, 1385.

As stated above, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

Thus the present invention further provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

In a further aspect of this invention, there is provided a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance.

Preferably, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are administered as pharmaceutically acceptable compositions.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

Neurotraumatic diseases include both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region, ischaemic stroke including acute stroke, particularly to the brain area, transient ischaemic attacks following coronary by-pass and cognitive decline following other transient ischaemic conditions.

The active compounds are usually administered as the sole medicament agent but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated. For example in the treatment of diabetes, especially Type 2 diabetes, a compound of formula (I), or a pharmaceutically acceptable derivative thereof, may be used in combination with other medicament agents, especially antidiabetic agents such as insulin secretagogues, especially sulphonylureas, insulin sensitisers, especially glitazone insulin sensitisers (for example thiazolidinediones), or with biguanides or alpha glucosidase inhibitors or the compound of formula (I), or a

pharmaceutically acceptable derivative thereof, may be administered in combination with insulin.

The said combination comprises co-administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil,

fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) or the above mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above mentioned reference texts.

GSK-3 Assays

Types of GSK-3 assay used to test the compounds of the invention include the following:

Type 1: The GSK-3 specific peptide used in this assay was derived from the phosphorylation site of glycogen synthase and its sequence is:

YRRAAVPPSPSLSRHSSPHQ(S)EDEEE. (S) is pre-phosphorylated as is glycogen synthase in vivo and the three consensus sites for GSK-3 specific phosphorylation are underlined. The buffer used to make up the glycogen synthase peptide and [γ-^{33}P] ATP consisted of MOPS 25mM, EDTA 0.2mM, MgAcetate 10mM, Tween-20 0.01% and mercaptoethanol 7.5mM at pH 7.00.

The compounds were dissolved in dimethyl sulphoxide (DMSO) to a final concentration of 100mM. Various concentrations were made up in DMSO and mixed with the substrate (GSK-3 peptide) solution (to a final concentration 20uM) described in the above section along with rabbit or human GSK-3α and GSK-3β (final concentration 0.5U/ml enzyme). The reactions were initiated with the addition of [γ-^{33}P] ATP (500cpm/pmole) spiked into a mixture of ATP (final concentration of 10μM). After 30 min at room temperature the reaction was terminated by the addition of 10μl of H_3PO_4 / 0.01% Tween-20 (2.5%). A volume (10μl) of the mixture was spotted onto P-30 phosphocellulose paper (Wallac & Berthold, EG&G Instruments Ltd, Milton Keynes). The paper was washed four times in H_3PO_4 (0.5%), 2 mins for each wash, air dried and the radioactive phosphate

incorporated into the synthetic glycogen synthase peptide, which binds to the P-30 phosphocellulose paper, was counted in a Wallac microbeta scintillation counter. Analysis of Data: Values for IC_{50} for each inhibitor were calculated by fitting a four-parameter logistic curve to the model : cpm=lower+(upper-lower) /(1 + (concentration/ IC_{50}) ^{slope}).

Type 2: This protocol is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot- KYRRAAVPPSPSLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads (Amersham Technology), where the signal from the ^{33}P is amplified via the scintillant contained in the beads. Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [^{33}P]-ATP. After incubation at room temperature, the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). IC_{50} values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show IC_{50} values in the range of 1 to 100 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Syntheses illustrate the invention, but do not limit it in any way.

Synthesis 1

3-[4-[3-(Carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A1)

A mixture of 3-(4-Aminophenylthio)phenylacetic acid (0.500 g, 1.93 mmol), 3-chloro-4-(4-chlorophenyl)-1H-pyrrole-2,5-dione (0.200 g, 0.80 mmol) and 1-methyl-2-pyrrolidinone (4.0 mL) was heated in a sealed tube in a hotblock set at 69°C for 28.5 hours. The mixture was diluted with aqueous hydrochloric acid (10 mL) and extracted with ethyl acetate (2x20 mL). The combined organics were washed with brine (2x10 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using a gradient of dichloromethane-methanol as eluent to give a solid.

^1H NMR (DMSO-d_6): δ3.55 (2H,s), δ6.82 (3H, m), δ7.09 (8H, m), δ9.88 (1H, s), δ10.98 (1H, s), δ12.39 (1H, bs).

MS (APCI +ve): $[M+H]^+$ at m/z 467 ($C_{24}H_{16}F_2N_2O_4S$ requires $[M+H]_+$ at m/z 467.

Synthesis 2

3-[4-[3-(Methylaminocarbonylmethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A2)

Methylamine (0.08mL, 2M in tetrahydrofuran, 0.17mmol) was added to a solution of 3-[4-[3-(carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table A, Example A1; 0.070 g, 0.16 mmol), 1-hydroxybenzotriazole (0.022 g, 0.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.031 g, 0.17 mmol in dichloromethane (2.5 mL). The mixture was stirred at ambient temperature for 18h. Saturated aqueous sodium bicarbonate (5 mL) was added, stirring continued for 5 minutes and the organic layer transferred directly onto a column of silica gel. Elution with dichloromethane-methanol gave the product as a solid.

^{1}H NMR (DMSO-d_6): δ2.54 (3H, d), δ3.36 (2H, s), δ6.80 (3H, m), δ7.14 (8H, m), δ7.94 (1H, bq), δ9.88 (1H, s), δ10.98 (1H, s).

MS (APCI +ve): $[M+H]^+$ at m/z 480 ($C_{25}H_{19}F_2N_3O_3S$ requires $[M+H]^+$ at 480).

Synthesis 3

3-[4-[3-(Aminocarbonylmethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A3)

A solution of N-hydroxysuccinimide (1.0g, 8.70 mmol) in methanol (15mL) was treated with methanolic ammonia and the resulting ammonium salt was collected by filtration and dried in vacuo. A mixture of this ammonium salt (0.035 g, 0.27 mmol) and 3-[4-[3-(Carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table A, Example A1; 0.100 g, 0.20 mmol) in dimethylformamide (5 mL) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (0.057 g, 0.27 mmol) was added. The mixture was allowed to warm to ambient temperature and stirred for 18 h. The dimethylformamide was removed in vacuo, the residue taken up in ethyl acetate (5 mL) and the insoluble material removed by filtration. The filtrate was concentrated and the residue chromatraphed on silica gel using a gradient of dichloromethane-methanol as eluent to give a solid.

^{1}H NMR (DMSO-d_6): δ3.34 (2H, s), δ6.77 (3H, m), δ6.79 (1H, bs), δ7.09 (8H, m), δ7.42 (1H, bs), δ9.88 (1H, s), δ10.98 (1H, s).

MS (APCI +ve): $[M+H]^+$ at m/z 466 ($C_{24}H_{17}F_2N_3O_3S$ requires $[M+H]^+$ at m/z 466).

Synthesis 4

3-[4-[3-(N-Hydroxyaminocarbonylmethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A4)

O-(*tert*-Butyldimethylsilyl)hydroxylamine (0.029 g, 0.20 mmol) was added to a solution of 3-[4-[3-(Carboxymethyl)phenylthio]phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table A, Example A1; 0.100 g, 0.20 mmol), 1-hydroxybenzotriazole (0.027 g, 0.20 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.041 g, 0.20 mmol in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 18h. Water (5 mL) was added and the mixture extracted into ethyl acetate (3x10 mL). Concentration of the organic solutions gave a residue which was purified by chromatography on silica gel, eluting with a gradient of dichloromethane-methanol to give a solid.

^{1}H NMR (DMSO-d_6): δ3.30 (2H, s), δ6.78 (3H, m), δ7.10 (8H, m), δ8.85 (1H, s), δ9.88 (1H, s), δ10.63 (1H, s), δ10.98 (1H, bs).

MS (APCI +ve): $[M+H]^+$ at m/z 482 ($C_{24}H_{17}F_2N_3O_4S$ requires $[M+H]^+$ at m/z 482).

Synthesis 5

3-[3-[(1,3-Thiazolidin-2,4-dion-5-yl)methyl]phenylamino]-4-(2,3,5-trifluorophenyl)-1H-pyrrole-2,5-dione (Example C1)

A solution of 5-[(3-aminophenyl)methyl]-1,3-thiazolidine-2,4-dione (277mg, 1.25 mmol) and 3-chloro-4-(2,3,5 trifluorophenyl)-1H-pyrrole-2,5-dione (131mg, 0.5mmol) in methanol (2 mL) was heated at 69°C for 5 days. EtOAc (6ml) was added and heating continued for a further 1hr. The mixture was acidified with aqueous hydrochloric acid (1M, 10mL) and extracted with ethyl acetate (10 mL). The organic solution was washed with water (3 x 10mL), brine, dried with magnesium sulphate, evaporated and the residue chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 100:0 to 75:25 v/v) as eluent to afford the title compound, a solid.

^{1}H NMR (DMSO-d_6):

δ2.75 (1H, dd), δ3.05 (1H, dd), δ4.67 (1H, dd), δ6.60-7.40 (6H, m), δ9.95 (1H, s), δ11.00 (1H, s) and δ12.05 (1H, br).

MS (APCI +ve): $[M+H]^+$ at m/z 448 ($C_{20}H_{12}F_3N_3O_4S$ requires $[M+H]^+$ at m/z 448).

Synthesis 6

3-[[2-(2-Carboxyethyl)pyridin-5-yl]amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example E1)

A mixture of 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.100 g, 0.41 mmol), 3-(5-aminopyridin-2-yl)propanoic acid (0.170 g, 1.02 mmol) and 1-methyl-2-pyrrolidinone (2.0 mL) was heated in a sealed tube in a hotblock set at 69°C for 14 days. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (2x60 mL). The combined organics were washed with water (80 mL), brine (80 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was triturated with a mixture of dichloromethane-hexane (80:20 v/v) to afford the title compound, a solid.

^{1}H NMR (DMSO-d_6): δ2.44-2.50 (2H, m), δ2.69-2.80 (2H, m), δ6.85-7.09 (4H, m), δ7.16-7.26 (1H, m), δ7.96 (1H, s), δ9.83 (1H, s), δ10.95 (1H,s) and δ12.05 (1H, br).

MS (APCI +ve): $[M+H]^+$ at m/z 374 ($C_{18}H_{13}F_2N_2O_4$ requires $[M+H]^+$ at m/z 374).

Synthesis 7

3-(3-Aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C38)

3-(3-Nitrophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C36; 0.350 g, 1.01 mmol) and 10% Pd/C (50 mg) in ethanol (40 mL) was hydrogenated at atmospheric temperature and pressure for 2 hours. The reaction mixture was filtered through Kieselguhr and the filtrate concentrated in vacuo to give a solid which was triturated with a mixture of dichloromethane-hexane (20:80 v/v) to afford the title compound, a solid.

^{1}H NMR (DMSO-d_6): δ4.88 (2H, s), δ5.77 (1H, d), δ6.10-6.13 (2H, m), δ6.50 (1H, t), δ6.88-7.06 (2H, m), δ7.13-7.23 (1H, m), δ9.55 (1H, s), δ10.82 (1H, t). MS (APCI +ve): $[M+H]^+$ at m/z 316 ($C_{16}H_{11}F_2N_3O_2$ requires $[M+H]^+$ at m/z 316).

Synthesis 8

3-[4-(Benzoylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A18)

A mixture of 3-(4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C35; 0.100 g, 0.31 mmol), benzoic acid (0.042 g, 0.35 mmol), 1-hydroxybenzotriazole (0.047 g, 0.34 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.067 g, 0.34 mmol) in dimethylformamide (3 mL) was shaken on an orbital shaker for 72 hours. The mixture was diluted with aqueous hydrochloric acid (1M, 100 mL), and extracted with ethyl acetate (2x60 mL). The combined organic solutions were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over anhydrous magnesium sulphate and evaporated. Trituration of the residue with dichloromethane-hexane (20:80 v/v) gave the title product, a solid.

^{1}H NMR (DMSO-d_6): δ6.77 (2H, d), δ6.96-7.17 (2H, m), δ7.17-7.27 (1H, d), δ7.40-7.60 (5H, m), δ7.88 (2H, d), δ9.75 (1H, s), δ10.00 (1H, s), δ10.85 (1H, br).

MS (APCI –ve): $[M-H]^-$ at m/z 418 ($C_{23}H_{15}F_2N_3O_3$ requires $[M-H]^-$ at m/z 418)

Synthesis 9

3-[4-(tert-Butoxycarbonylmethylcarbonylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C49)

A mixture of 3-(4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C35; 0.100 g, 0.31 mmol), mono-tert-butyl malonate (0.056 g, 0.35 mmol), 1-hydroxybenzotriazole (0.047 g, 0.34 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.067 g, 0.34 mmol) in dimethylformamide (3 mL) was shaken on an orbital shaker for 72 hours. The mixture was diluted with dilute hydrochloric acid (100 mL), and extracted with ethyl acetate (2x60 mL). The combined organics were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using dichloromethane-diethyl ether (90:10 v/v) as eluent to afford the the title product, a solid.

^{1}H NMR (DMSO-d_6): δ1.40 (9H, s), δ3.27 (2H, s), δ6.72 (2H, d), δ6.93-7.09 (2H, m), δ7.16-7.24 (3H, m), δ9.75 (1H, br), δ10.00 (1H, s), δ10.85 (1H, br).

MS (APCI –ve): $[M-H]^-$ at m/z 456 ($C_{23}H_{21}F_2N_3O_5$ requires $[M-H]^-$ at m/z 456).

Synthesis 10

3-[4-(Carboxymethylcarbonylamino)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C53)

A mixture of 3-[4-(tert-butoxycarbonylmethylcarbonylamino)phenyl--amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C49; 0.040 g, 0.087 mmol), trifluoroacetic acid (30 mL) and dichloromethane (50 mL) was stirred at

room temperature for 40 minutes. The mixture was evaporated and the residue was diluted with water (80 mL), basified to ca. pH 3-4 with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (2x70 mL). The combined organic solutions were quickly washed with saturated aqueous sodium bicarbonate (40 mL), brine (100 mL), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was triturated with a mixture of dichloromethane-hexane (20:80 v/v) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ3.27 (2H, s), δ6.72 (2H, d), δ6.93-7.09 (2H, m), δ7.17-7.26 (3H, m), δ9.75 (1H, s), δ10.03 (1H, s), δ10.87 (1H, s), δ12.60 (1H,br).

MS (APCI –ve): $[M-H-CO_2]^-$ at m/z 356 ($C_{19}H_{13}F_2N_3O_5$ requires $[M-H-CO_2]^-$ at m/z 356).

Synthesis 11

3-(2,3,4-Trifluorophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C39)

A mixture of 2,3,4-trifluoroaniline (0.184 g, 1.25 mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.122 g, 0.5 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was heated in a sealed tube in a hotblock set at 69°C for 20 hours then at 90°C for a further 4 days. The mixture was diluted with aqueous hydrochloric acid (20 mL) and extracted with ethyl acetate (20 mL). The organics were washed with hydrochloric acid (20 mL), water (3x20 mL), and evaporated to dryness. The residue was chromatographed on silica gel using dichloromethane then dichloromethane-diethyl ether (50:1 v/v) as eluent to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ6.7 – 7.3 (6H, m), δ9.8 (1H, br), δ10.95(1H, br).

MS (APCI +ve): $[M+H]^+$ at m/z 355 ($C_{16}H_7F_5N_2O_2$ requires $[M+H]^+$ at m/z 355).

Synthesis 12

3-[(2-Methylbenzoxazol-6-yl)amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example B6) and

3-[(4-acetamido-3-hydroxyphenyl)amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C63)

A mixture of 6-amino-2-methylbenzoxazole (0.185 g, 1.25 mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.122 g, 0.5 mmol) in methanol (3mL) was heated in a sealed tube in a hotblock set at 69°C for 20 hours. The mixture was diluted with aqueous hydrochloric acid (20 mL) and extracted with ethyl acetate (20 mL). The organics were washed with water (3x10 mL), and evaporated to dryness. The residue was triturated with diethyl ether to afford a solid which was dissolved in dichloromethane/methanol and chromatographed on silica gel using dichloromethane-diethyl ether (25:1 v/v) as eluent to afford 3-[(2-methylbenzoxazol-6-yl)amino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table B, Example B6) as a solid.

^{1}H NMR (DMSO-d_6): δ2.50 (3H, s, obscured by DMSO solvent peak), δ6.7 – 7.3 (6H, m), δ10.0 (1H, br), δ10.8(1H, br).

MS (APCI +ve): $[M+H]^+$ at m/z 356 ($C_{18}H_{11}F_2N_3O_3$ requires $[M+H]^+$ at m/z 356).

Further elution of the chromatography column afforded 3-(3-hydroxy-4-acetamidophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C63) as a byproduct.

Synthesis 13

3-(3-Trifluoromethyl-4-acetamidophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C28) and

3-(3-trifluoromethyl-4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C27)

A solution of 3-trifluoromethyl-4-acetamidoaniline (273mg, 1.25 mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (122mg, 0.5mmol) in methanol (2 mL) was heated at 69°C for 3 days. EtOAc (6ml) was added and heating continued for a further 1hr. The mixture was acidified with aqueous hydrochloric acid (1M, 10mL) and extracted with ethyl acetate (10 mL). The organic solution was washed with water (3 x 10mL), brine, dried with magnesium sulphate, evaporated and the residue chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 100:0 to 75:25 v/v) as eluent to afford 3-(3-trifluoromethyl-4-acetamidophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C28) as a solid.

^{1}H NMR (DMSO-d_6): δ1.97 (3H, s), δ6.7-7.3 (6H, m), δ9.37 (1H, s), δ10.00 (1H, br), δ10.92 (1H, br).

MS (APCI +ve): $[M+H]^+$ at m/z 426 ($C_{19}H_{12}F_5N_3O_3$ requires $[M+H]^+$ at m/z 426).

Earlier fractions from the chromatography column yielded 3-(3-trifluoromethyl-4-aminophenylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table C, Example C27) as a byproduct.

Synthesis 14

3-[2-(Methoxymethyl)indolin-1-yl]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example D6)

A solution of 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (195 mg, 0.80 mmol.), 2-(methoxymethyl)indoline (198 mg, 1.00 mmol.) and triethylamine (0.34 mL, 2.44 mmol.) in dry 1-methylpyrrolidin-2-one (3 mL) was heated under argon at 65 C for 3 days. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic solutions were washed with brine (2 x 20 mL), dried with magnesium sulphate, evaporated and the residue chromatographed on silica using a mixture of dichloromethane and diethyl ether as eluant to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 11.05 (1H, br), 7.36-7.13 (4H, m), 6.79 (1H, t), 6.61 (1H, t), 5.86 (1H, d), 5.26 (1H, m), 3.69 (1H, m), 3.35 (2H, m), 3.26 (3H, s), 3.00 (1H, dd).

MS (APCI+ve): $[M+H]^+$ at m/z 371 ($C_{20}H_{16}N_2O_3F_2$ requires $[M+H]^+$ at m/z 371).

Synthesis 15

3-[3-(4-Carboxyphenylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A50)

A mixture of 4-(3-aminophenylacetylamino)benzoic acid (0.277 g, 1.03 mmol), 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (0.100 g, 0.41 mmol) and 1-methyl-2-pyrrolidinone (2 mL) was heated at 110°C overnight before being diluted with dilute hydrochloric acid (2M, 150 mL) and extracted with ethyl acetate (3 x 80 mL). The combined ethyl acetate solutions were washed with brine, dried ($MgSO_4$) and evaporated. The residual solid was chromatographed on silica gel using dichloromethane-methanol (96:4 v/v) as eluent to afford the title compound, a solid.

^{1}H NMR (DMSO-d_6): δ3.30 (2H, s), δ6.65-7.20 (7H, m), δ7.66 (2H, d), δ7.85 (2H, d), δ9.75 (1H, s), δ10.30 (1H, s), δ10.85 (1H, s) and δ12.62 (1H, s).

MS (AP-ve): $[M]^-$ at m/z 477 ($C_{25}H_{17}F_2N_3O_5$ requires $[M]^-$ at m/z 477).

Synthesis 16

3-[2-(Ethylamino)benzothiazol-6-ylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example B48)

A solution of 2-ethylaminobenzothiazol-6-ylamine (316mg, 1.63mmol) and 3-chloro-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (158mg, 0.65mmol) in 1-methyl-2-pyrrolidinone (2mL) was allowed to stand at room temperature overnight. The mixture was diluted with aqueous hydrochloric acid (25mL) and extracted with ethyl acetate (35 mL). The organics were washed with water (3x25mL), and evaporated to dryness. The residue was triturated with dichloromethane to give a solid.

^{1}H NMR (DMSO-d_6): δ1.16 (3H,t), δ3.31 (2H, m), δ6.73 (1H, m), δ6.95 (4H, m), δ7.1 (1H, m), δ7.86 (1H, t), δ9.70(1H, bs), δ10.80 (1H, bs).

MS (APCI +ve): $[M+H]^+$ at m/z 401 ($C_{19}H_{14}F_2N_4O_2S$ requires $[M+H]^+$ at m/z 401.

Synthesis 17

3-[3-(4-Pyrimidylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example F17)

A mixture of 4-aminopyrimidine (48mg, 0.5mmol), 3-[3-(carboxymethyl)-phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (prepared by analogy with Example Synthesis 1, 179mg, 0.5mmol), 1-hydroxybenzotriazole (68mg, 0.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96mg, 0.5mmol) was dissolved in dimethylformamide (2mL). The solution was allowed to stand at room temperature for 5 days. Ethyl acetate (8mL), water (4mL) and saturated aqueous sodium bicarbonate (2 mL) were added, the layers separated and the organic layer washed with water then brine and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-methanol to give the product as a solid.

^{1}H NMR (DMSO-d_6): δ3.39 (2H, m), δ6.6 – 7.2 (7H,m), δ8.00 (1H, m), δ8.6 (1H, m), δ8.85 (1H, s), δ9.76 (1H, s), δ10.9 (1H, s) and δ11.0 (1H, s).

MS (APCI +ve): $[M+H]^+$ at m/z 436 ($C_{22}H_{15}F_2N_5O_3$ requires $[M+H]^+$ at 436).

Synthesis 18

3-[3-(3-Carboxyphenylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A91)

A mixture of 3-[3-(carboxymethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (prepared by analogy with Example Synthesis 1,179mg, 0.5mmol), 1-hydroxybenzotriazole (68mg, 0.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96mg, 0.5mmol) was dissolved in dimethylformamide (2mL). After standing at room temperature for 1 hour, 3-aminobenzoic acid (69mg, 0.5mmol) was added and the resulting solution was allowed to stand at room temperature for 2 days. Ethyl acetate (8mL) and water (6mL) were added, the layers separated and the organic layer washed with water (3x6mL) and evaporated to a gum which was triturated with dichloromethane/methanol to give the product as a solid.

^{1}H NMR (DMSO-d_6): δ3.28 (2H, s), δ6.73 (2H,m), δ6.95 (4H, m), δ7.15 (1H, m), δ7.41(1H, m), δ7.60 (1H, m), δ7.80(1H, m), δ8.19 (1H, s), δ9.77 (1H, s), δ10.2 (1H, s), δ10.9(1H, s), δ12.9 (1H, bs).

MS (APCI -ve): $[M]^-$ at m/z 477 ($C_{25}H_{17}F_2N_3O_5$ requires $[M]^-$ at 477).

Synthesis 19

3-(3,5-Difluorophenylamino)-4-(4-acetylaminophenyl)-1H-pyrrole-2,5-dione (Example C97)

A mixture of 3-(3,5-difluorophenylamino)-4-(4-nitrophenyl)-1H-pyrrole-2,5-dione (Table C, Example C91, 0.012 g, 0.035 mmol), stannous chloride dihydrate (0.023 g, 0.105 mmol) and ethanol (5 mL) was stirred at 70°C overnight before being evaporated and suspended in dichloromethane. The resulting precipitate was collected and suspended in dichloromethane (5 mL) and treated with acetic anhydride (10 uL, 0.1 mmol). The mixture was stirred for 70 hours then chromatographed on silica gel using dichloromethane-methanol (90:10 v/v) as eluent to afford the title compound, a solid.

^{1}H NMR (DMSO-d_6): δ2.02 (3H,s), δ6.33 (2H, m), δ6.65 (1H, m), δ6.98 (2H, d), δ7.41 (2H, s), δ9.60 (1H, bs), δ9.90 (1H, s) and δ10.90 (1H, s).

MS (AP-ve): $[M]^-$ at m/z 357 ($C_{18}H_{13}F_2N_2O_3$ requires $[M]^-$ at m/z 357).

Synthesis 20

3-(Indolin-5-ylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example B46)

A mixture of 3-(N-t-butoxycarbonylindolin-5-ylamino)-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Table B, Example B45, 0.100 g, 0.22 mmol), trifluoroacetic acid (0.5 mL) and dichloromethane (9.5 mL) was stirred at room temperature for 2 hours, then evaporated. The residue was azeotroped from dichloromethane (x3) to afford the product, a solid.

^{1}H NMR (DMSO-d_6): δ2.73 (2H, t), δ3.55 (2H, t), δ3.98 (1H, br), δ6.60-7.30 (6H, m), δ9.77 (1H, s), and δ10.90 (1H, s).

MS (AP+ve): $[M+H]^+$ at m/z 342 ($C_{18}H_{13}F_2N_3O_2$ requires $[M+H]^+$ at m/z 342).

Synthesis 21

3-[3-(N-Hydroxylaminocarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example C106)

A mixture of O-(tert-butyldimethylsilyl)hydroxylamine (221mg, 1.5mmol), 3-[3-(carboxymethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (prepared by analogy with Example Synthesis 1, 179mg, 0.5mmol), 1-hydroxy-7-azabenzotriazole (136mg, 1mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144mg, 0.75mmol) was dissolved in dimethylformamide (2mL). The solution was allowed to stand at room temperature for 4 days. Ethyl acetate (8mL) and water (8mL) were added and the mixture acidified to pH3 with dilute hydrochloric acid. The layers were separated and the organic layer washed with water (2x8mL), saturated aqueous sodium bicarbonate (8mL) then water (2x8mL) and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-methanol to give a solid (38mg). This was dissolved in tetrahydrofuran (3mL), tetrabutylammonium fluoride trihydrate (49mg, 0.156mmol) added and the solution stirred at room temperature for 30 mins. The resulting suspension was evaporated to dryness, the residue dissolved in ethyl acetate (10mL) and water (10mL) and acidified to pH3 with dilute hydrochloric acid. The layers were separated and the organic layer washed with water (2x10mL) and evaporated to give the product as a solid.

^{1}H NMR (DMSO-d_6): δ2.87 (2H, s), δ6.61 (1H,s), δ6.71 (1H, m), δ6.81 (1H, m), δ7.0 (3H, m), δ7.15 (1H, m), δ8.74 (1H, bs) and δ9-11 (3H, broad).

MS (APCI -ve): $[M-H]^-$ at m/z 372 ($C_{18}H_{13}F_2N_3O_4$ requires $[M-H]^-$ at 372).

Synthesis 22

3-[3-(2-(4-Aminophenylsulphonyl)ethoxycarbonylmethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (Example A70)

A mixture of 2-(4-aminophenylsulphonyl)ethanol hydrochloride (119mg, 0.5mmol), 3-[3-(carboxymethyl)phenylamino]-4-(2,3-difluorophenyl)-1H-pyrrole-2,5-dione (179mg, 0.5mmol), 1-hydroxybenzotriazole (68mg, 0.5mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96mg, 0.5mmol) and triethylamine (101mg, 1mmol) in dimethylformamide (2mL) was well shaken then allowed to stand at room temperature for 3days. Ethyl acetate (8mL), water (4mL) and saturated aqueous sodium bicarbonate (2 mL) were added, the layers separated and the organic layer washed with water then brine and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-methanol to give the product as a solid.

^{1}H NMR (DMSO-d_6): δ2.99 (2H, s), δ3.57 (2H,t), δ4.23 (2H, t), δ5.69 (2H, s), δ6.49 (1H, s), δ6.75 (2H, m), δ6.8-7.1 (6H, m), δ7.1-7.3 (2H, m) δ9.73 (1H, s), δ10.9 (1H, s).

MS (APCI +ve): $[M+H]^+$ at m/z 542 ($C_{26}H_{21}F_2N_3O_6S$ requires $[M+H]^+$ at 542).

The following additional methods (Methods 1 and 2) serve to illustrate a typical preparation of a non-commercial aniline by a method analogous to that described in *Synthesis* 1994, 1413.

Method 1

3-[(4-Nitrophenyl)thio]benzoic acid

A suspension of potassium carbonate (18g) in acetone (140 mL) at ambient temperature was treated with 3-mercaptobenzoic acid (10g, 64.4 mmol, 1 eq) followed by 4-nitrofluorobenzene (18g, 127.7 mmol, 2 eq). The resultant mixture was stirred for 18h and then poured onto saturated sodium bicarbonate and washed with ethyl acetate. The basic aqueous layer was acidified with 5N HCl and extracted into ethyl acetate (3x100 mL). The combined organics were dried with anhydrous sodium sulphate and concentrated *in vacuo* to give the product as a solid.

^{1}H NMR (DMSO): δ7.35 (2H, d), 7.66 (1H, t), 7.81 (1H, m), 8.06 (2H, m), 8.16 (2H, d), and 13.31 (1H. bs).

MS (APCI-ve): $[M-H]^-$ at m/z 274 ($C_{13}H_9NO_4S$ requires $[M-H]^-$ at m/z 274)

Method 2

3-[(4-Aminophenyl)thio]benzoic acid

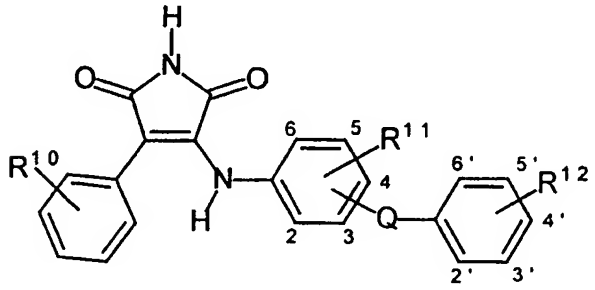
A mixture of 3-[(4-nitrophenyl)thio]benzoic acid (11.2g, 40.7 mmol) and 10% Pd/C (0.5g) in ethanol (250 mL) was hydrogenated at atmospheric temperature and pressure for 24h. The mixture was filtered through Celite and concentrated *in vacuo* to give the required aniline as a solid. ^{1}H NMR (DMSO): δ5.59 (2H, bs), 6.64 (2H, d), 7.28 (3H, m), 7.37 (1H, t), 7.52 (1H, s), 7.65 (1H, d), and 12.32 (1H, bs).MS (APCI+ve): $[M+H]^+$ at m/z 246 ($C_{13}H_{11}NO_2S$ requires $[M+H]^+$ at m/z 246).

The further examples described herein were prepared according to the methods disclosed herein, with particular reference to Example Syntheses 1 to 22 above. Example Syntheses 1 to 22 themselves are shown as Example Compounds in the following Tables according to the list below:

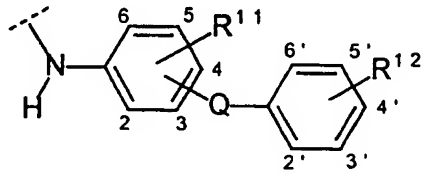
Synthesis No.	Table	Example No.
1	A	A1
2	A	A2
3	A	A3
4	A	A4
5	C	C1
6	E	E1
7	C	C38
8	A	A18
9	C	C49
10	C	C53
11	C	C39
12 12 (Byproduct)	B C	B6 C63
13 13 (Byproduct)	C C	C28 C27
14	D	D6
15	A	A50
16	B	B48
17	F	F17
18	A	A91
19	C	C97
20	B	B46
21	C	C106
22	A	A70

Table A

Encompassing compounds of general formula (Z-1), wherein group R^2 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{10} and the moiety NR^1R^3 of formula (I) is represented by a moiety of general formula (Z-2), optionally substituted by one or more substituents R^{11} and one or more substituents R^{12}, and Q represents a linking moiety as hereinbefore defined. The positions of substitution of R^{11}, R^{12} and Q are defined with reference to formula (Z-2) and the values of R^{10}, R^{11}, R^{12} and Q are listed in Table A.



(Z-1)



(Z-2)

Example No.	R^{10}	R^{11}	Q	R^{12}	$[M+H]^+$ Observed; (Unless $[M]^-$ or $[M-H]^-$ are Indicated)	For Procedure See Example No.
A1	2,3-di-F	H	4-[S]	3'-CH2CO2H	467	1
A2	2,3-di-F	H	4-[S]	3'-CH2CONHMe	480	2
A3	2,3-di-F	H	4-[S]	3'-CH2CONH2	466	3
A4	2,3-di-F	H	4-[S]	3'-CH2CONHOH	482	4

A5	2,3-di-F	H	4-[S]	3'-CONHMe	466	2
A6	2,3-di-F	3-CO2H	4-[S]	3'-CONHMe	510	2
A7	2,3-di-F	H	4-[O]	3'-CO2H	437	1
A8	2,3-di-F	H	3-[CH2CONH]	H	432 [M-H]-	5
A9	2,3-di-F	H	4-[CH2CONH]	H	434	5
A10	2,3-di-F	H	3-[CO]	H	405	5
A11	2,3-di-F	H	3-[OCH2]	H	407	5
A12	2,3-di-F	H	4-[NHCO]	2'-OH	436	5
A13	2,3-di-F	3-CO2Et	4-[S]	2'-CO2H	525	5
A14	2,3-di-F	H	4-[O]	3'-CONHMe	450	2
A15	2,3-di-F	H	4-[O]	3'-CONH2	434[M-H]-	3
A16	2,3-di-F	H	4-[S]	3'-CONH2	452	3
A17	2,3-di-F	H	4-[O]	4'-CONHMe	450	5
A18	2,3-di-F	H	4-[NHCO]	H	418 [M-H]-	8
A19	2,3-di-F	H	4-[S]	3'-CONH(CH2)2OMe	510	2
A20	2,3-di-F	3-CO2H	4-[S]	2'-CO2H	495 [M-H]-	1
A21	2,3-di-F	H	4-[NHCOCH2]	H	434	8
A22	2,3-di-F	H	3-[NHCOCH2]	H	432 [M-H]-	8
A23	2,3-di-F	H	3-[NHCO]	H	418 [M-H]-	8
A24	2,3-di-F	H	4-[O]	4'-CO2H	437	5
A25	2,3-di-F	3-CO2H	4-[S]	H	453	1

A26	2,3-di-F	H	4-[CH2NHCOCH2]	H	446 [M-H]-	8
A27	2,3-di-F	3-CONHMe	4-[S]	H	466	2
A28	2,3-di-F	H	4-[O]	4'-CONH2	436	3
A29	2,3-di-F	H	4-[S]	3'-[CH2CONH(CH2)2-Morpholin-4-yl]	579	1
A30	2,3-di-F	H	3-[SO2NH]	H	456	5
A31	2,3-di-F	H	3-[CH2NHCO]	H	432 [M-H]-	8
A32	2,3-di-F	H	4-[NHSO2]	4'-Me	468 [M-H]-	1
A33	2,3-di-F	H	3-[CH2NHCOCH2]	H	446 [M-H]-	8
A34	2,3-di-F	H	4-[NHCOCH2CH2]	H	446 [M-H]-	8
A35	3-CN	H	4-[S]	3'-CO2H	440 [M-H]-	1
A36	2,3-di-F	H	4-[O]	2'-CO2H	437	1
A37	2,3-di-F	3-CO2H	4-[bond]	H	419 [M-H]-	1
A38	2,3-di-F	H	4-[S]	2'-CH2CO2Me	481	1
A39	2,3-di-F	H	4-[S]	4'-CONH2	452	3
A40	2,3-di-F	3-CO2H	4-[S]	4'-CO2H	495 [M-H]-	1

A41	2,3-di-F	H	4-[O]	2'-CONHMe	448 [M-H]-	2
A42	2,3-di-F	H	4-[CH2CONH]	3'-CO2H	476 [M-H]-	1
A43	2,3-di-F	H	4-[O]	3'-CH2CO2H	451	1
A44	2,3-di-F	H	4-[S]	2'-CO2H	451 [M-H]-	1
A45	2,3-di-F	H	4-[O]	2'-CONH2	435 [M]-	2
A46	2,3-di-F	H	4-[S]	4'-CONHMe	466	2
A47	2,3-di-F	H	4-[S]	2'-CONH2	451 [M]-	3
A48	2,3-di-F	H	4-[S]	2'-CONHMe	464 [M-H]-	2
A49	2,3-di-F	H	4-[CH2CONH]	4'-CO2H	477 [M]-	15
A50	2,3-di-F	H	3-[CH2CONH]	4'-CO2H	477 [M]-	15
A51	2,3-di-F	3-CO2H	4-[O]	H	436 [M]-	15
A52	2,3-di-F	3-CO2H	4-[O]	4'-Ph	512 [M]-	15
A53	2,3-di-F	H	3-[CONH]	4'-CO2H	462 [M-H]-	15
A54	2,3-di-F	H	3-[CH2O]	4'-CO2H	449 [M-H]-	1
A55	2,3-di-F	H	4-[CH2SO2NH]	H	468 [M-H]-	5
A56	2-F-3-Cl	H	4-[O]	4'-CO2H	451/453 [M-H]-	1
A57	2,3-di-F	H	3-[O]	4'-CO2H	435 [M-H]-	1
A58	2,3-di-F	H	3-[O]	4'-CH2CO2H	451	15
A59	2,3-di-F	H	4-[O]	4'-CH2CO2H	449 [M-H]-	15
A60	2,3,6-tri-F	H	4-[O]	4'-CO2H	453 [M-H]-	1

A61	2,3-di-F	H	3-[CH2CONH]	4'-CH2CH2OH	478	17
A62	2-Cl-3-F	H	4-[O]	4'-CO2H	451, 453 [M-H]-	1
A63	2,3-di-F	H	3-[O]	3'-CO2H	437	15
A64	2,3-di-F	H	3-[O]	4'-CH2CH2CO2H	465	15
A65	2,3-di-F	H	3-[CH2CONH]	4'-Morpholin-4-yl	519	17
A66	2,3-di-F	H	3-[CH2CONH]	4'-Piperidin-1-yl	517	17
A67	2,3-di-F	H	3-[CH2CONH]	4'-CH2OH	463 [M-]	17
A68	2,3-di-F	H	4-[O]	3'-NMe2	436	1
A69	2,3-di-F	H	3-[OCH2]	4'-CO2H	449 [M-H]-	1
A70	2,3-di-F	H	3-[CH2CO2-CH2CH2SO2]	4'-NH2	542	22
A71	2,3-di-F	H	3-[CH2CONH]	4'-NMe2	477	17
A72	2,3-di-F	H	3-[CH2CONH]	3'-Cl-4'-Morpholin-4-yl	552/554 [M-]	17
A73	2,3-di-F	H	3-[CH2CONH]	4'-CH2CN	473	17
A74	2,3-di-F	H	3-[CH2CONH]	4'-OCH2-(1-Me-Piperidin-4-yl)	561	17

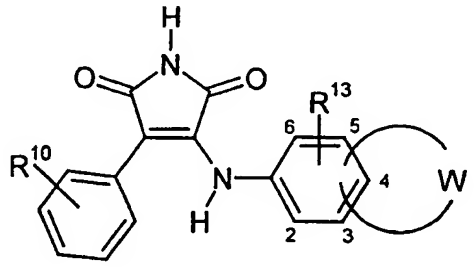
A75	2,3-di-F	H	3-[O]	3'-NH2	408	1
A76	2,3-di-F	H	4-[O]	4-NHCOMe	450	1
A77	2,3-di-F	3-Me	4-[O]	4'-CH2CO2H	464 [M]-	1
A78	2,3-di-F	H	4-[CH2SO2NH]	4'-CO2H	512 [M-H]-	1
A79	2,3-di-F	H	4-[O]	3'-NHCOMe	450	1
A80	2,3-di-F	H	3-[CH2CONH]	3'-NHCOMe	491	17
A81	2,3-di-F	H	3-[CH2CONH]	4'-NHCOMe	491	17
A82	2,3-di-F	H	3-[CH2CONH]	4'-N(Me)COMe	504 [M-]	17
A83	2,3-di-F	H	3-[CH2CONH]	3'-CONH2	477	17
A84	2,3-di-F	H	3-[CH2CONH]	2'-CONH2	476 [M-]	17
A85	2,3-di-F	H	3-[CH2CONH]	3'-NMe2	477	17
A86	2,3-di-F	H	4-[CH2SO2NH]	4'-CH2CO2H	526 [M-H]-	1
A87	2,3-di-F	H	4-[CH2SO2NH]	3'-CH2CO2H	526 [M-H]-	1
A88	2,3-di-F	H	4-[CH2SO2NH]	3'-CO2H	512 [M-H]-	1
A89	2,3-di-F	3-Cl	4-[O]	4'-CH2CO2H	483/485 [M-H]-	1
A90	2,3-di-F	3-Cl	4-[O]	4'-CO2H	469/471 [M-H]-	1
A91	2,3-di-F	H	3-[CH2CONH]	3'-CO2H	477 [M-]	18

A92	2,3-di-F	H	3-[CH2CONHCH2]	4'-NMe2	491	17
A93	2,3-di-F	H	3-[CH2CONHNHCO]	4'-NH2	491 [M-]	17
A94	2,3-di-F	H	4-[O]	4'-CH2NHCOMe	464	1
A95	4-Cl	3-CO2H	4-[O]	4'-Cl	469/471/473	5
A96	2,3-di-F	H	3-[O]	4'-NHCOMe	450	1
A97	2,3-di-F	H	3-[CH2CONH]	4'-CONH2	475 [M-H]-	17
A98	2,3-di-F	H	4-[O]	3'-NHCONH2	449 [M-H]-	1
A99	2,3-di-F	H	4-[O]	4'-CH2CH2NMe2	464	1
A100	2,3-di-F	H	3-[CH2CONH]	3'-NH2	449	17
A101	2,3-di-F	H	3-[CH2CONH]	4'-NH2	449	17
A102	2,3-di-F	H	3-[CH2CONHNHCO]	H	477	17
A103	2,3-di-F	H	3-[CH2CONH]	4'-SO2NH2	513	17
A104	2,3-di-F	H	3-[CH2CONH]	3'-CH2OH	462 [M-H]-	17

A105	2,3-di-F	H	3-[CH2CONH(CH2)2]	4'-NH2	477	17
A106	2,3-di-F	H	3-[CH2CONHNHCO]	3'-NH2	492	17
A107	2,3-di-F	H	3-[CH2SO2NH]	H	468 [M-H]-	1
A108	2,3-di-F	H	3-[CH2SO2NH]	3'-CO2H	512 [M-H]-	1
A109	2,3-di-F	H	3-[CH2CONH]	4'-NHSO2Me	527	17
A110	2,3-di-F	H	3'-[CH2SO2NH]	4'-CO2H	512 [M-H]-	1
A111	2,3-di-F	H	3-[SO2]	3'-NH2	456	1
A112	2,3-di-F	H	4-[O]	4'-SO2NH2	470 [M-H]-	1
A113	2,3-di-F	H	4-[O]	4'-NH2	406 [M-H]-	1
A114	2,3-di-F	H	4-[CH2SO2NH]	4'-NHSO2Me	563	1
A115	2,3-di-F	H	4-[CH2SO2NH]	4'-NHCOMe	525 [M-H]-	1

Table B

Encompassing compounds of general formula (Z-3), wherein group R^2 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{10} and the group R^1 is represented by a benzene ring fused to an additional ring wherein the moiety W represents the atoms which, when taken together with the atoms of the benzene ring to which they are attached, form the fused ring. The position of the fusion of the two rings is defined with reference to the atom numbering depicted in formula (Z-3), for example in the case of compound B1, the moiety W has the value 3,4-[S-CH=N] and is defined as having the sulphur atom of the moiety attached at position 3 and the nitrogen atom attached at position 4 to form a 5-membered thiazole ring. Additionally, the benzene ring may be optionally substituted by one or more additional substituents R^{13}. The group R^3 of formula (I) is hydrogen. The values of R^{10}, R^{13} and W are listed in Table B.



(Z-3)

Example No.	R^{10}	R^{13}	W	$[M+H]^+$ Observed; (Unless $[M]^-$ or $[M-H]^-$ are Indicated)	For Procedure See Example No.
B1	3-CN	H	3,4-[S-CH=N]	347	5
B2	2,3-di-F	H	3,4-[CH2CH2N(SO2Me)]	420	5
B3	2,3,6-tri-F	H	3,4-[CH2CH2CH2]	359	5
B4	2,3-di-F	H	3,4-[N=C(Me)-S]	372	5
B5	2,3-di-F	H	3,4-[S-C(Me)=N]	372	5

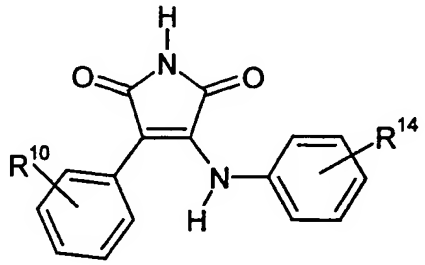
B6	2,3-di-F	H	3,4-[O-C(Me)=N]	356	12
B7	2,3-di-F	H	3,4-[N=C(Me)-O]	356	1
B8	2,3-di-F	H	3,4-[O-CH=N]	342	1
B9	2,3-di-F	H	3,4-[CH=CH-N(Me)]	354	1
B10	2,3-di-F	H	3,4-[O-C(=O)-NH]	358	1
B11	3-CO2H	H	3,4-[S-CH=N]	364 [M-H]-	1
B12	2,3-di-F	H	3,4-[S-C(SCH2CO2Me)=N]	462	5
B13	2,3-di-F	H	3,4-[S-C(SCH2CO2H)=N]	448	1
B14	3-CH2OH	H	3,4-[S-CH=N]	350 [M-H]-	5
B15	2,3-di-F	H	3,4-[CH=CH-CH=N]	352	1
B16	2,3-di-F	H	3,4-[S-C(=O)-NH]	372 [M-H]-	1
B17	2,3-di-F	H	3,4-[N(Me)-CH=N]	355	1
B18	2,3-di-F	H	3,4-[S-C(Cl)=N]	392/394	1
B19	2,3-di-F	H	3,4-[S-C(SMe)=N]	404	14
B20	2-F-3-Cl	H	3,4-[S-CH=N]	372/374 [M-H]-	5
B21	2,3-di-F	H	3,4-[NHCONH]	357	14
B22	2,3-di-F	H	3,4-[S-C(Ph)=N]	434	1
B23	2,3-di-F	H	3,4-[S-C(NHMe)=N]	387	14
B24	2,3-di-F	H	3,4-[S-C(NMe2)=N]	401	1
B25	2,3-di-F	H	3,4-[S-C(=O)N(CH2CO2Me)]	446	1
B26	2,3-di-F	H	3,4-[S-C(=O)N(CH2CO2H)]	432	1
B27	2,3-di-F	H	3,4-[CH=CH-S]	357	1
B28	2,3-di-F	H	3,4-[S-C[S(CH2)3CO2H]=N]	476	1

B29	2,3-di-F	H	3,4-[S-C(NHPh)=N]	449	1
B30	2,3-di-F	H	3,4-[N(Me)CON(Me)]	385	1
B31	2,3-di-F	H	3,4-[S-CO-N(Me)]	388	1
B32	2,3-di-F	H	3,4-[S-C[(CH2)4CO2Me]=N]	472	1
B33	2,3-di-F	H	3,4-[S-C[(CH2)4CO2H]=N]	458	1
B34	2-Cl-3-F	H	3,4-[S-CH=N]	372/374 [M-H]-	5
B35	2,3,6-tri-F	H	3,4-[S-CH=N]	374 [M-H]-	5
B36	2,3-di-F	H	3,4-[CH=C(CO2H)-O]	384 [M]-	1
B37	2,3-di-F	H	3,4-[S-C[NH(CH2)3NMe2]=N]	458	16
B38	2,3-di-F	H	3,4-[S-CO-N[(CH2)3NMe2]]	459	1
B39	2,3-di-F	H	3,4-[S-C(Morpholin-4-yl)=N]	443	1
B40	2,3-di-F	H	3,4-[S-CO-N(3-F-Ph)]	468	15
B41	2,3-di-F	H	3,4-[S-CO-N(4-OMe-Ph)]	480	15
B42	2,3-di-F	H	3,4-[S-CO-N(CH2Ph)]	464	5
B43	2,3-di-F	H	3,4-[S-CO-N(3-NHCOMe-Ph]	507	1
B44	2,3-di-F	H	3,4-[CH=C(CO2H)-N(Me)]	396 [M-H]-	1
B45	2,3-di-F	H	3,4-[CH2CH2N(CO2t-Bu)]	440 [M-H]-	5
B46	2,3-di-F	H	3,4-[CH2CH2NH]	342	20
B47	2,3-di-F	H	3,4-[CH2CONH]	356	1
B48	2,3-di-F	H	3,4-[S-C(NHEt)=N]	401	16

B49	2,3-di-F	H	3,4-[S-C(NH2)=N]	373	1
B50	2,3-di-F	H	3,4-[S-C(NHi-Pr)=N]	415	1
B51	2,3-di-F	H	3,4-[NH-CO-O]	358	1
B52	2,3-di-F	H	3,4-[CH=C(CONH2)-N(Me)]	395 [M-H]-	1
B53	2,3-di-F	H	3,4-[OCH2CONH]	370 [M-H]-	14
B54	2,3-di-F	H	3,4-[S-C(NHCOMe)=N]	415	1

Table C

Encompassing compounds of general formula (Z-4), wherein group R^2 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{10}, group R^1 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{14} and group R^3 of formula (I) is hydrogen, and substituents R^{10} and R^{14} are listed in Table C.



(Z-4)

Example No.	R^{10}	R^{14}	$[M+H]^+$ Observed; (Unless $[M]^-$ or $[M-H]^-$ are Indicated)	For Procedure See Example No.
C1	2,3,5-tri-F	3-[CH2-(1,3-thiazolidine-2,4-dion-5-yl)]	448	5
C2	3,5-di-Me	3,5-di-F	327 [M-H]-	5
C3	2,3,6-tri-F	3-Cl	353/355	5
C4	2,3-di-F	3-OCH2CO2H	375	1
C5	3-CN	H	290	5
C6	3-CN	3,5-di-F	324 [M-H]-	5
C7	2,3-di-F	3-CONHMe-4-NHMe	387	5
C8	2,3-di-F	4-[CH2CO(4-Me-Piperazin-1-yl)]	441	5
C9	2,3-di-F	2-(Morpholin-4-yl)	386	5
C10	2,3-di-F	3-[CH2CO(Morpholin-4-yl)]	428	5
C11	2,3-di-F	3-[CH2CO(Piperidin-1-yl)]	426	5

C12	2,3-di-F	4-[CH2CO(Piperidin-1-yl)]	426	5
C13	2,3-di-F	4-[CH2CONH(CH2)2OH]	402	5
C14	2,3-di-F	4-[CH2CONMe2]	386	5
C15	2,3-di-F	3-CONHMe-4-Cl	392/394	5
C16	2,3-di-F	3-SO2NH(CH2)2OMe	438	5
C17	2,3-di-F	3-SO2NH*n*Bu	436	5
C18	2,3-di-F	3-COMe	343	5
C19	3-F	3-CH2CO2H	341	1
C20	2,3-di-F	3-NHCOMe	358	5
C21	2,3-di-F	4-NHCOCF3	412	5
C22	2,3-di-F	2-Me	315	5
C23	2,3-di-F	2-Me-4-F	333	5
C24	2,3-di-F	2-Me-5-F	333	5
C25	2,3-di-F	3-Me	315	5
C26	2,3-di-F	2-SMe	347	5
C27	2,3-di-F	3-CF3-4-NH2	384	13
C28	2,3-di-F	3-CF3-4-NHCOMe	426	13
C29	2,3,6-tri-F	4-CH2SO2NHMe	426	5
C30	2,3,6-tri-F	4-CH2CH2CONH2	390	5
C31	2,3,6-tri-F	3,5-di-F	355	5
C32	2,3,6-tri-F	4-Me	333	5
C33	2,3,6-tri-F	H	319	5
C34	2,3-di-F	3-[CH2CONH(CH2)2NMe2]	429	5
C35	2,3-di-F	4-NH2	316	5
C36	2,3-di-F	3-NO2	344 [M-H]-	11
C37	2-Cl-5-F	3-Cl	351/353/355	5
C38	2,3-di-F	3-NH2	316	7
C39	2,3-di-F	2,3,4-tri-F	355	11
C40	2,3-di-F	3-F-5-CF3	385 [M-H]-	11

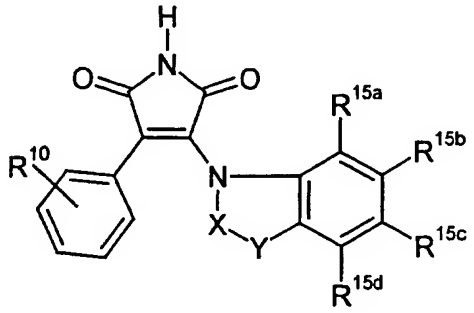
C41	2,3-di-F	4-O(CH2)3CO2H	403	1
C42	2,3-di-F	4-CH2NHCO2*t*Bu	428 [M-H]-	1
C43	3-CN	4-*trans*-CH=CHCONH2	357 [M-H]-	1
C44	2,3-di-F	4-NHCOCH2OMe	386 [M-H]-	8
C45	2,3-di-F	4-NHCOCH2NHCOMe	415	8
C46	2,3-di-F	4-CH2NHCO*n*Pr	400	8
C47	2,3-di-F	4-NHCOCH2OH	374	8
C48	2,3-di-F	3-NHCOCH2OMe	388	8
C49	2,3-di-F	4-NHCOCH2CO2*t*Bu	456 [M-H]-	9
C50	2,3-di-F	3-NHCOCH2NHCOMe	413 [M-H]-	8
C51	3-CO2H	H	307 [M-H]-	1
C52	2,3-di-F	4-NHCO*n*Pr	384 [M-H]-	8
C53	2,3-di-F	4-NHCOCH2CO2H	356 Fragment ion [M-CO2H]-	10
C54	2,3-di-F	4-CH2NHCOCH2OMe	400 [M-H]-	8
C55	2,3-di-F	4-CH2NHCOCH2NHCOMe	427 [M-H]-	8
C56	3-CN	4-(CH2)3CO2H	374 [M-H]-	1
C57	3-CO2H	4-(CH2)3CO2H	393 [M-H]-	1
C58	2,3-di-F	3-CH2NHCO2*t*Bu	428 [M-H]-	11
C59	2,3-di-F	4-CH2NHCOCH2OH	386 [M-H]-	8
C60	3-CO2H	3,5-di-F	343 [M-H]-	1
C61	3-CO2H	4-NHCOMe	364 [M-H]-	1
C62	2,3-di-F	3-NHCOCH2OH	372 [M-H]-	8
C63	2,3-di-F	3-OH-4-NHCOMe	374	12
C64	2,3-di-F	4-CH2NHCOCH2CO2*t*Bu	470 [M-H]-	9
C65	3-CO2H	3-CH2CONH2	364 [M-H]-	1
C66	2,3-di-F	3-SO2NH2	378 [M-H]-	5
C67	2,3-di-F	3-CH2NHCOCH2OMe	400 [M-H]-	8

C68	2,3-di-F	3-CH2NHCOCH2NHCOMe	429	8
C69	2,3-di-F	3-CH2NHCOCH2OH	386 [M-H]-	8
C70	3-CH2OH	H	293 [M-H]-	5
C71	2,3-di-F	4-*trans*-CH=CHCO2H	369 [M-H]-	1
C72	2,3-di-F	4-NHCO(CH2)2CONH2	413 [M-H]-	8
C73	2,3-di-F	4-O(CH2)3CONHMe	416	5
C74	3-CN	4-NHCOMe	345 [M-H]-	5
C75	3-CN	4-CH2SO2NHMe	395 [M-H]-	5
C76	2,3-di-F	4-CH2SO2NMe2	420 [M-H]-	5
C77	3-CN	3-CH2CONH2	345 [M-H]-	5
C78	3-CH2OH	4-CH2SO2NHMe	400 [M-H]-	5
C79	3-CH2OH	3,5-di-F	329 [M-H]-	5
C80	2,3-di-F	4-[CH2-(1,3-thiazolidine-2,4-dion-5-yl)]	430	5
C81	2,3-di-F	3-CH2CH2CO2H	373	1
C82	2,3,6-tri-F	4-CH2CH2CH2CO2H	403 [M-H]-	1
C83	2-F-3-Cl	4-CH2CH2CH2CO2H	401/403 [M-H]-	1
C84	2-F-3-Cl	3,5-di-F	351/353 [M-H]-	5
C85	2,3-di-F	4-OH	315 [M-H]-	5
C86	2,3,6-tri-F	3,5-di-Cl-4-OH	401/403/405 [M-H]-	5
C87	2-F-3-Cl	3,5-di-Cl-4-OH	399/401/403/405 [M-H]-	5
C88	2-Cl-3-F	3,5-di-Cl-4-OH	399/401/403/405 [M-H]-	5
C89	2-Cl-3-F	4-(CH2)3CO2H	401/403 [M-H]-	1
C90	2-Cl-3-F	3,5-di-F	351/353 [M-H]-	5
C91	4-NO2	3,5-di-F	344 [M-H]-	5
C92	4-I	3,5-di-F	425 [M-H]-	5

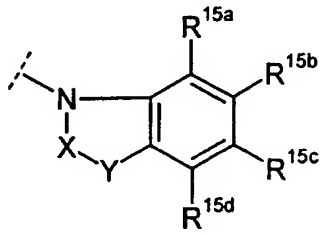
C93	2,3-di-F	3-F-4-OCH2CO2H	393	1
C94	2,3-di-F	4-NHCOCO2H	342 [M-H-CO2]-	1
C95	2-Cl	3-[CH2-(1,3-thiazolidine-2,4-dion-5-yl)]	428/430	5
C96	2,3-di-F	3-Me-4-*trans*-CH=CHCO2H	383 [M-H]-	1
C97	4-NHCOMe	3,5-di-F	357 [M]-	19
C98	2,3-di-F	3-CH2CONHNHCOMe	415	17
C99	2,3-di-F	4-(CH2)4NHCOMe	414	5
C100	2,3-di-F	4-(CH2)4NHSO2Me	448 [M-H]-	5
C101	2,3-di-F	3-CH2NHSO2Me	406 [M-H]-	5
C102	2,3-di-F	4-CH2CH2P(O)(OEt)OH	435 [M-H]-	1
C103	2,3-di-F	4-CH2CH2SO2NH2	407 [M]-	5
C104	2,3-di-F	3-CH2SO2NH2	392 [M-H]-	1
C105	2,3-di-F	3-CH2CONHOMe	386 [M-H]-	17
C106	2,3-di-F	3-CH2CONHOH	372 [M-H]-	21
C107	2,3-di-F	4-trans-CH=CHCONHOMe	400	1
C108	2,3-di-F	4-CH2NH2	330	20
C109	2,3-di-F	3-CH2NH2	330	20

Table D

Encompassing compounds of general formula (Z-5), wherein group R^2 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{10} and the moiety -NR^1R^3 of formula (I) represents a heterocyclyl moiety of general formula (Z-6), optionally substituted by substituents R^{15a}, R^{15b}, R^{15c} and R^{15d} and substituents R^{10}, R^{15a}, R^{15b}, R^{15c}, R^{15d} and X-Y are listed in Table D.



(Z-5)

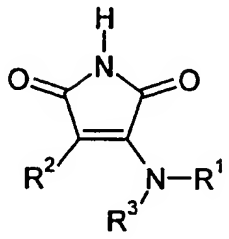


(Z-6)

Example No.	R^{10}	R^{15a}	R^{15b}	R^{15c}	R^{15d}	X-Y	$[M+H]^+$ Observed; (Unless $[M]^-$ or $[M-H]^-$ are Indicated)	For Procedure See Example No.
D1	2,3-di-F	H	H	H	H	CH(CH2OH)CH2 (S)-Isomer	357	5
D2	2,3,6-tri-F	H	H	H	H	(CH2)2	345	5
D3	2,3-di-F	H	H	H	H	(CH2)3	341	5
D4	3,5-di-Me	H	H	H	H	(CH2)3	333	5
D5	2-Cl	H	H	H	H	(CH2)3	339/341	11
D6	2,3-di-F	H	H	H	H	CH(CH2OMe)CH2	371	14

Table E

Encompassing compounds of general formula I, and substituents R^1 R^2 and R^3 are listed in Table E.

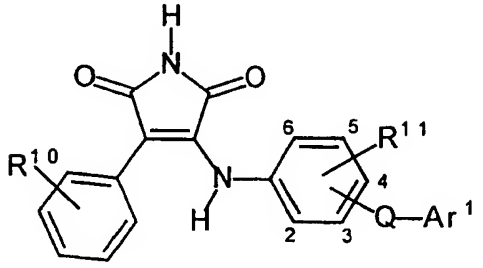


(I)

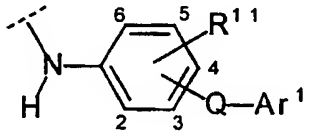
Example No.	R^1	R^2	R^3	$[M+H]^+$ Observed; (Unless $[M]^-$ or $[M-H]^-$ are Indicated)	For Procedure See Example No.
E1	2-[(CH2)2CO2H]-Pyridin-5-yl	2,3-di-F-Ph	H	374	6
E2	2-[(CH2)3CN]-3-Me-Pyridin-5-yl	2,3-di-F-Ph	H	383	6
E3	2-Me-Pyridin-3-yl	2,3-di-F-Ph	H	316	6
E4	2-[(CH2)3CN]-3-(CO2Et)-Pyridin-5-yl	2,3-di-F-Ph	H	441	6
E5	2-[(CH2)4CO2H]-Pyridin-5-yl	2,3-di-F-Ph	H	402	6
E6	2-[(CH2)3CN]-Pyridin-3-yl	2,3-di-F-Ph	H	369	6
E7	2-(OPh)-Pyridin-5-yl	2,3-di-F-Ph	H	394	15

Table F

Encompassing compounds of general formula (Z-7), wherein group R^2 of formula (I) is a phenyl ring, optionally substituted by one or more substituents R^{10} and the moiety NR^1R^3 of formula (I) is represented by a moiety of general formula (Z-8), optionally substituted by one or more substituents R^{11}. Q represents a linking moiety and Ar^1 represents an aromatic heterocyclic group as hereinbefore defined. The positions of substitution of R^{11} and Q are defined with reference to formula (Z-8) and the values of R^{10}, R^{11}, Q and Ar^1 are listed in Table F.



(Z- 7)



(Z- 8)

Example No.	R^{10}	R^{11}	Q	Ar^1	$[M+H]^+$ Observed; (Unless $[M]^-$ or $[M-H]^-$ are Indicated)	For Procedure See Example No.
F1	2,3-di-F	H	3-[bond]	5-Oxazolyl	368	5
F2	2,3-di-F	H	4-[NHCO(CH2)2]	3-Pyridinyl	449	8
F3	2,3-di-F	H	4-[bond]	5-Me-2-Oxazolyl	382	5
F4	2,3-di-F	H	4-[bond]	2-Me-4-Oxazolyl	382	5
F5	2,3-di-F	H	4-[bond]	6-Me-Benzothiazol-2-yl	448	5

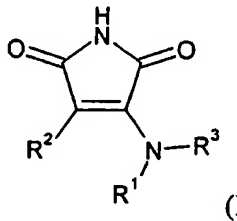
F6	2,3-di-F	H	4-[O]	3-Pyridinyl	392 [M-H]-	15
F7	2,3-di-F	4-OH	3-[bond]	Benzothiazol-2-yl	450	14
F8	2,3-di-F	H	3-[CH2CONH]	Quinolin-3-yl	485	17
F9	2,3-di-F	H	4-[bond]	3-Me-1,2,4-Oxadiazol-5-yl	381 [M-H]-	5
F10	2,3-di-F	H	3-[CH2CONH]	2-Me-Pyridin-3-yl	449	17
F11	2,3-di-F	H	3-[CH2CONH]	5-Me-Pyridin-3-yl	449	17
F12	2,3-di-F	H	3-[CH2CONH]	2-OMe-Pyridin-5-yl	465	17
F13	2,3-di-F	H	3-[CH2CONH]	Pyridin-3-yl	435	17
F14	2,3-di-F	H	3-[CH2CO2CH2]	3-NH2-Pyridin-2-yl	465	22
F15	2,3-di-F	H	4-[O(CH2)2NMe]	Pyridin-2-yl	451	1
F16	2,3-di-F	H	4-[OCH2]	Pyridin-3-yl	408	1
F17	2,3-di-F	H	3-[CH2CONH]	Pyrimidin-4-yl	436	17
F18	2,3-di-F	H	3-[CH2CONH]	Pyrazin-2-yl	436	17
F19	2,3-di-F	H	4-[O]	Pyridin-2-yl	392 [M-H]-	5
F20	2,3-di-F	H	4-[bond]	2-OH-Pyrimidin-5-yl	393 [M-H]-	5

F21	2,3-di-F	H	4-[bond]	5-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl	409 [M-H]-	5
F22	2,3-di-F	H	4-[bond]	2,5-di-Me-4,5-dihydro-2H-pyridazin-3-on-6-yl	423 [M-H]-	5
F23	2,3-di-F	H	4-[bond]	1H-Pyrazol-3-yl	365 [M-H]-	5
F24	2,3-di-F	H	4-[SCH2]	1H-Imidazol-4-yl	413	5
F25	2,3-di-F	H	3-[CH2SO2NH]	Pyridin-3-yl	471	1
F26	2,3-di-F	H	4-[bond]	2-OMe-Pyrazin-5-yl	409	5
F27	2,3-di-F	H	4-[bond]	1H-Pyrazin-2-on-5-yl	395	5
F28	2,3-di-F	H	4-[bond]	5,6-Dihydro-4H-[1,3,4]-Oxadiazin-5-on-2-yl]	397 [M-H]-	5
F29	2,3-di-F	H	4-[bond]	4,5-dihydro-2H-pyridazin-3-on-6-yl	395 [M-H]-	5
F30	2,3-di-F	H	4-[bond]	2H-pyridazin-3-on-6-yl	393 [M-H]-	5

5

Claims

1. A method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof,
wherein;

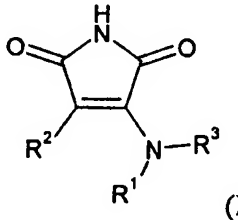
R^1 is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic or non-aromatic ring;

R^2 is a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, which ring may be fused to a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring, with the proviso that R^2 is not 3-indolyl or a fused-ring derivative of 3-indolyl;

R^3 is hydrogen, or,

R^1 and R^3 together with the nitrogen atom to which they are attached form a fused substituted or unsubstituted heterocylic ring;
to a human or non-human mammal in need thereof.

2. A compound of formula (I')



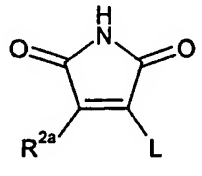
(I')

wherein;

R^1, R^2, and R^3 are as defined in formula (I) in claim 1, with the proviso that formula (I') does not include the following compound:

3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione.

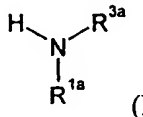
3. A process for the preparation of a compound of formula (I'), which process comprises reaction of a compound of formula (II)



(II)

wherein;

R^{2a} is as defined for R^2 in formula (I) in claim 1 and L is a leaving group, with a compound of formula (III)



(III)

wherein;

R^{1a} and R^{3a} are as defined for R^1 and R^3 respectively in formula (I) in claim 1, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I') to a further compound of formula (I');

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

4. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

5. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and manic depression, hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, inflammation and immunodeficiency.

6. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance.

7. A pharmaceutical composition which comprises a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 01/03687

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/44 C07D401/12 C07D417/12 C07D403/12 C07D413/12
C07D409/12 C07D407/12 C07D403/04 C07D401/04 A61K31/4015
A61K31/4025 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 06564 A (JAPAN TOBACCO INC ;INABA TAKASHI (JP); SAKODA KENJI (JP); TANAKA M) 10 February 2000 (2000-02-10) abstract -& EP 1 120 414 A (JAPAN TOBACCO INC) 1 August 2001 (2001-08-01) page 8 -page 15 table 57 claim 14 ---	1-7
X	US 3 340 263 A (CIBA SA) 5 September 1967 (1967-09-05) column 2, line 22 - line 27 column 2, line 50 - line 66 examples 1-4 claim 3 --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2001	07/09/2001

Name and mailing address of the ISA	Authorized officer
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